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The effectiveness of a guided online mindfulness-based intervention for the prevention of stress in a student population: Study protocol for a randomized control trial

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Abstract

Background: Previous studies and surveys showed that university students experience a higher psychological stress level than the general population, which results in a higher vulnerability for mental disorders. To increase individuals' mental health and to offer flexibility, mindfulness as an online intervention seems to be a promising approach. This study aims to investigate the effectiveness of a guided online mindfulness-based intervention for university students with the use of questionnaires and psychobiological measures.

Methods and analyses: In this multicenter, two-armed randomized controlled trial (RCT) with a parallel design, a guided version of the online mindfulness-based intervention "StudiCare Mindfulness" will be compared to a waitlist control group. In total, 120 participants will be recruited at different universities (of Applied Sciences) in (Neu-) Ulm. Data will be assessed prior to randomization, after eight weeks (post-intervention) and six months after randomization (follow-up). The primary outcome is mindfulness, measured by the Freiburg Mindfulness Inventory. Secondary outcomes include depression-, anxiety- and stress level, well-being, interoceptive sensibility, emotion regulation, and alexithymia. Psychobiological parameters comprise interoceptive accuracy, hair cortisol, and FKBP5 genotype. Sociodemographic variables, treatment expectations, side, and adverse effects, as well as intervention satisfaction and adherence, will also be assessed. All data analyses will be conducted according to the Intention-To-Treat (ITT) principle.

Ethics and dissemination: All study procedures have been approved by the ethics committee of Ulm University (application No. 48/18). The findings will be disseminated widely through peer-reviewed publications and conference presentations.

Trial registration: fpatient

Keywords: RCT, eHealth, online intervention, stress, mindfulness, effectiveness

Strengths and limitations of this study

- "StudiCare Mindfulness" is an online mindfulness-based intervention program to increase mindfulness and simultaneously decrease stress level in order to reduce mental disorders in university students.
- This study considers psychobiological parameters additional to the common participants´ self-report data prior to randomization as well as eight weeks and six months after randomization.
- To assess the long-term effect of the intervention a follow-up measurement after six months after randomization is administered.

- Because of the use of psychobiological parameters, the study will only be conducted at universities (of Applied Sciences) in (Neu-) Ulm, which could reduce generalizability.

Background

Stress is highly prevalent among university students. Previous studies showed significantly higher stress levels compared to the general population [e.g., 1–3]. The increased stress level of university students seems to result from being confronted with new experiences and challenges on top of being exposed to a variety of stressors (e.g., new social relationships, academic pressure, exams), which can exhibit a clinical level of distress [2, 4–7]. Moreover, such high stress levels have the potential to trigger or exacerbate symptoms of mental health conditions [8–10]. As a result, university students can develop mental disorders, such as anxiety or depression [11–16]. For example, Auerbach and co-workers [11] stated in an international WHO-survey that more than 20 percent of university students report a mental disorder. Similar results were found in another survey, indicating that 23 percent of the university students meet the criteria for a mental disorder [17]. The development of mental disorders is related to a more severe and chronic disease trajectory, a higher risk to develop comorbidities and a decreased academic performance, as well as an increased probability for dropouts [5, 9, 18–20].

Accordingly, it is crucial to prevent elevated stress levels and decrease mental health disabilities in university students. In this context, previous studies revealed that most university students do not use face-to-face interventions and do not seek professional help, although most of the universities provide free health and counseling service [e.g., 8, 16, 21–26]. As common reasons university students mention lack of time, fear of stigma, the preference to get help and support from family or friends as well as lack of knowledge regarding available services at the university. Thus, internet- and mobile-based psychological interventions (IMIs) are a promising approach to close the gap between these barriers and to provide additional advantages (e.g., no need of therapist availability, low-threshold access, stigma-reduction, cost-effectiveness as well as flexibility regarding time and place) [22, 23, 27–31]. Emerging evidence from different studies has also demonstrated that online interventions can be as effective as face-to-face programs [32–34]. Furthermore and most importantly, nowadays young people grow up in a digital world and prefer using the internet as well as smartphones daily [35–37]. They are also searching for health information online [38]. However, a study with an Australian sample (mean age 36.6 years) showed that 77.1% prefer face-to-face intervention [39]. In another study by Ryan and colleagues [26], findings indicate that nearly 50% of university students (mean age 23.7) have a preference for online interventions. Consequently, the age range and the context seems to be crucial for the results, showing a higher preference in a university sample – additionally, the preference growth due to an increasing distress level [26].

Moreover, Stallman and Kavanagh [40] as well as Ebert and co-workers [27], observed that university students show a high acceptance and usability for online interventions. A growing body of research found that online interventions are helpful to improve mental health conditions [e.g., 27, 41–46]. These effects can be enhanced by therapeutic guidance [6, 47].

One opportunity to improve mental and physical health is mindfulness. It is described as the awareness of the present moment in an open, accepting and non-judgmental way with the focus on one's breathing and other bodily sensations [48–50]. Several studies found positive effects of the mindfulness-based intervention on mental and physical health conditions, independent of whether these included healthy or clinical participants [51–59]. Furthermore, Wahbeh and colleagues [59] showed a preference of individuals for online mindfulness-based interventions compared to a group or one-by-one interventions. Regarding the benefits of mindfulness – especially on mental health – and online interventions in general as well as the growing research in the field of e-health and e-mental health programs, it seems timely to combine these approaches to reduce stress and therefore to improve mental health in a student population.

Numerous studies [e.g., 44, 60–63] and meta-analyses [64, 65] found evidence for the efficacy of online mindfulness-based interventions with the focus on self-reported health variables (e.g., depression, anxiety, and stress). For example, Spijkerman, Pots and Bohlmeijer [64] compared 15 randomized control trials and showed small to medium effect sizes regarding the improvement of depression (g = .29, 95% CI: .13 - .46), anxiety (g = .22; 95% CI: .05 - .39), well-being (g = .23; 95% CI .09 - .38) and mindfulness (g = .32, 95% CI .23 - 42) in healthy samples as well as samples with mental disorders. Especially, for stress a large effect could be shown (g = .51; 95% CI: .26 - .75). Similar results were found in another meta-analysis of Jayewardene, Lohrmann, Erbe, and Torabi [65], comparing eight studies focusing on the intervention effect of online mindfulness interventions in populations with subclinical mental health conditions for non-clinical populations (g = .28 - .42; 95% CI: .15 - .67). Moreover, these results mostly increased for the follow-up measurement (g = .47 - .70; CI: .14 - 1.13). Even though these findings are promising, self-report data might substantially overestimate the effectiveness of interventions. Hence, the field should move forward to include more objective data, to verify the promising results, by including assessments of psychobiological variables.

Until now, there are no studies regarding the effect of online mindfulness-based training on psychobiological variables, which represent objective markers of mental health conditions. Such variables are not influenced by social desirability, problems regarding the memory or a conscious perception [66]. Consequently, psychobiological data are more reliable in comparison to self-reported data and should, therefore, accomplish self-report data in mindfulness and stress-related intervention studies. In this study, we include interoceptive

accuracy as well as cortisol and dehydroepiandrosterone (DHEA). Interoceptive accuracy represents the behavioral assessment to investigate the ability to perceive internal bodily changes [67] and is associated with different other health-related variables such as emotion perception and regulation, stress, depression, and eating behavior [68–73]. Recent studies focusing on interoceptive accuracy have shown mixed results regarding the impact of different offline mindfulness interventions [74–76]. Two biological indicators of the body's physiological stress response are cortisol and DHEA. While cortisol is a steroid hormone released by the hypothalamic-pituitary-adrenalin (HPA) axis in response to stress [77], DHEA represent an endogenous steroid hormone on the stress response that can antagonize the effect of cortisol [78]. To assess long-term effects of stress, collecting hair samples is superior to fluid biomaterial (e.g., saliva, blood), because hair samples reflect the stress level of weeks or even months and are not influenced by acute stress before or during the measurements or body's circadian rhythm as well as hormone level [79–82]. Accordingly, the ratio between cortisol and DHEA seems to be important. Several studies reveal inconsistent results concerning the effect of mindfulness interventions on stress parameters assessed by saliva or plasma cortisol [e.g., 83–88]. Moreover, there is no evidence in previous research of mindfulness training on DHEA. However, some studies measured the sulfated form of DHEA (DHEA-S) and found no effect on DHEA-S after an 8-week mindfulness-based stress program in a population diagnosed with cancer. To combine both stress markers, different researcher suggest the cortisol/DHEA ratio as a parameter for the endocrine imbalance of HPA regulation [89–93]. Comparable with DHEA, there is only one study that has investigated the cortisol/DHEA-S ratio. It indicated that men diagnosed HIV-positive had an improved ratio after participating in a cognitive-behavioral stress management program in comparison to a waitlist control group [92]. To sum up, studies examining psychobiological parameters in mindfulness-based programs are very sparse, though there are some promising results from cognitive-behavioral programs. Nonetheless, such investigations are essential to characterize the long-term effects of mindfulness on psychobiological processes better.

An additional focus of the present trial is the effectiveness of guidance during the online mindfulness-based intervention. Research in this context provides evidence that guided online intervention enhances the efficacy of health-related variables [64, 94]. In the context of online mindfulness training for students, only the study of Mak and colleagues [61] provided telephone or email support without a control group.

Taken together, we hypothesize that

1) The primary outcome *mindfulness* will be improved after the intervention in comparison to a waitlist control group.

2) The secondary outcomes of depression, anxiety- and stress level, life satisfaction, interoceptive sensibility, emotion regulation, and alexithymia will also be improved. We assume similar results for the psychobiological variables (secondary outcomes), including interoceptive accuracy as well as cortisol and DHEA levels in hair. Furthermore, we want to investigate the influence of the gene FKBP5 coding for FK506 binding protein 51 (FKBP51). FKBP51 is a co-chaperone of the glucocorticoid receptor, changing its affinity for cortisol and therefore influencing the reactivity of cortisol-mediated stress signaling in the body. Compared to C-allele carriers (wild type) at position rs1360780, individuals with the T-allele show a higher risk for depression and less clinical response to antidepressant treatment [95]. Also, T-allele carriers show more pronounced changes in hair cortisol levels with increasing childhood maltreatment compared to C-allele carriers, demonstrating a gen x environment interaction with a dose-response relationship between adverse childhood experiences, a strong predictor for late-life depression, and steroid hormones of the body's stress response [96].
3) The relationship between secondary outcomes and different covariates are also significant and need to be included in our analyses. It is especially necessary for the psychobiological variables (e.g., interoceptive accuracy can be influenced by emotion regulation, alexithymia or depression and anxiety symptoms [68, 71–73]). Lastly, we intend to analyze the participants' satisfaction, adherence, and acceptance of the intervention.

Methods

Study design

This project is a two-armed randomized controlled trial with a parallel design comparing the effectiveness of a guided version of the online, preventive mindfulness intervention "StudiCare Mindfulness" to a waitlist control group (see Fig. 1 for flowchart). The research aims to examine the effectiveness of StudiCare Mindfulness on different self-reported and psychobiological health-related parameters at three measurement points (before the intervention as well as eight weeks and six months after randomization). Moreover, the individuals' adherence, acceptance, and satisfaction are measured to identify possibilities to improve the intervention. Participants of both the control and the intervention group have access to treatment as usual. Thus, participants can use other support or treatment options that will be monitored in order to control for potential confounding effects.

The project takes part in collaboration with the Department for Clinical Psychology and Psychotherapy of Ulm University as one of two parallel mindfulness trials with a second trial investigating the effectiveness of a "guidance on demand" and an unguided version of "StudiCare Mindfulness" in comparison to a waitlist control group [97].

The present study is conducted and will be reported according to the CONSORT 2010 Statement [98] and the guidelines for executing and reporting internet intervention research [99]. The study protocol complies with recommendations of the SPIRIT 2013 Checklist for clinical trial protocols [100].

The "StudiCare Mindfulness" trial is carried out as part of the "StudiCare" project funded by BARMER, a cooperation of the Universities of Erlangen-Nuremberg and Ulm. The overall project aims an improving college university students' well-being by evaluating their mental health in longitudinal panel surveys as well as developing and offering a broad assortment of internet-based interventions for psychological and behavioral issues (such as procrastination, exam anxiety, physical activity). It is embedded in the "World Mental Health Survey International College Student" project (WMH-ICS) [101] as well as the "Caring Universities" project [102].

Patient involvement

College students as target end users of StudiCare Mindfulness were involved in the development process of the intervention. College students will also be involved in the conduct and the reporting of the research, however, not in their role as end user but in their role as scientists. The public will be informed about the results on several ways, amongst others publications, lectures and workshops.

Eligibility criteria

Participants providing written informed consent as well as fulfilling the following inclusion criteria for participation will be applied: a) age of 18 or above, b) enrolled at Universities (of Applied Sciences) in Ulm or Neu-Ulm, c) sufficient knowledge of the German language, d) internet access, e) moderate to low mindfulness (Freiburg Mindfulness Inventory FMI < 37); this cut-off was chosen as it represents the medium value of the FMI in subjects from the general population [103]. Participants are excluded from the study if they currently undertake psychotherapy or any mindfulness intervention. To investigate if participants are eligible, they have to fill out a screening questionnaire.

Setting/Recruitment

Recruitment has started in May 2018 and will be continued until the aimed sample size of 120 participants has been reached. Participants are only recruited at different universities in (Neu-) Ulm, including Ulm University, Ulm University of Applied Sciences and Neu-Ulm University of Applied Sciences because psychobiological parameters have to be assessed on-site. The following recruiting channels are used: email, flyer and poster, social media, student unions, and student counseling. University students get information about the "StudiCare" offers and a link to the homepage (www.studicare.com), where they can get further information and register for the IMIs. Once registered, they receive an email with a link to the screening. Depending on which University participants are from, they are either allocated to Kuechler et al.'s trial [97] (all other cooperating universities in Germany, Austria and Switzerland) or to the present study (students from different universities (of Applied Sciences) in Ulm and Neu-Ulm), as psychobiological tests demand actual attendance on-site). Once the screening is completed, participants receive an email with further information on the study as well as an informed consent form, which they are required to send back to the study staff via email. When written consent is obtained and the pretest completed, another email is sent to inform participants about their group (intervention or waitlist control group). If participants are part of the intervention group, they will also receive a link to the intervention. Participants are informed that "StudiCare Mindfulness" cannot replace psychotherapy and are recommended to seek counseling/psychotherapy in case of distinctive mental health problems. Additionally, they are provided with alternative treatment options and contact details (this information is also given to participants who do not meet the selection criteria).

Randomization

After completing the baseline assessment, participants are randomly allocated to one of two study groups (guided vs. waitlist control group) by an independent member of the Ulm University not otherwise involved and therefore blinded to all processes of the study. Via an automated, online-based randomization program (www.sealedenvelope.com), permuted block randomization is performed with an allocation ratio of 1:1 and variable block sizes of 2 and 4 (randomly arranged).

Intervention

The online mindfulness-based intervention consists of seven weekly, target-group-specific modules of approximately 60 min. each. Additionally, two booster sessions are activated four and twelve weeks after completion of the seventh module in order to ensure the sustainability of intervention effects. Beyond that, already completed sessions are accessible and can be repeated as often as participants wish to. All modules contain information on stress, well-being, and mindfulness with a weekly alternating focus on different topics such as interoception, dysfunctional and beneficial thinking or values and goals. Whereas these contents are

provided via texts, images and interactive elements (such as quizzes or conditional content), the focus of the intervention lies on the regular practice of mindfulness exercises such as body-scans, breathing meditations or mindful yoga. Therefore, each module includes downloadable audio files as well as mindfulness diaries to be complete in weekly homework assignments. At the beginning of each module, participants are encouraged to reflect their assignments and also their most and least mindful moments of the week. The content of the intervention is loosely based on the Acceptance and Commitment Theory [104] as well as stress management principles [e.g., 105]. The intervention's primary goal is to increase the student participants' mindfulness and psychological flexibility in order to enable them to manage their daily hassles flexibly. Furthermore, the intervention was developed by the Department of Clinical Psychology and Psychotherapy, Ulm University. Its efficacy has already been demonstrated in a randomized controlled trial [106]. Based on participants' feedback the different sessions were adapted and further refined. Moreover, the two weekly sessions ("Mindfulness body perception" and "Body and sense") were also extended. Table 1 summarizes the topics and contents of each module. The intervention is available for participants on the Minddistrict platform (www.minddistrict.com), a company specialized in the provision of internet-based health interventions. Participants can get access to the platform via their personal username and password on a 24/7 basis. All transferred data will be secured based on ISO27001 and guidelines NEN7510.

Table 1. Overview of the different topics and contents of each module

Module	Aims and content	Examples of exercises and assignments
1. Being in the here and now	Introducing the concept of mindfulness	Reviewing most and least mindful moments of the day; practicing Body Scan; taking mindful walks
2. Mindful body perception	Practicing awareness of body signals	Testing one's heartbeat perception; practicing "heart meditation"; mindful eating and drinking
3. A new perspective on stress	Distancing oneself from stress-inducing thoughts	Identifying former ways of coping with stress; learning techniques to challenge automatic thoughts; meditation exercise
4. Developing beneficial thoughts	Getting to know alternative ways of thinking	Identifying one's "stress patterns" and developing and internalizing beneficial thoughts; practicing breathing meditation
5. What makes your life valuable?	Identifying one's values and pursuing one's goals	Writing a speech for one's 70th birthday; setting and pursuing goals with the SMART technique; meditation exercise
6. Being mindful towards yourself	Learning how to accept one's personality traits appreciatively	Exercise to identify different personality traits and corresponding automatic reactions; learning to accept and appreciate all personality traits
7. Training your body and senses	Exercising the ability to enjoy and getting acquainted with the practice of yoga	Mindful chocolate eating exercise; mindful yoga exercises
Booster-Session 1	Repeating module 1 to 3 and mindfulness exercises	Choosing favorite mindfulness exercises; setting goals for their implementation in the coming weeks

(4 weeks after completion of module 7)		
Booster- Session 2 (12 weeks after completion of module 7)	Repeating modules 4 to 7 and ensuring long-term integration of mindfulness into daily life	Reviewing pursuit of goals in the last two months; identifying potential barriers and developing solutions

Guidance and promotion of adherence

Participants randomized to the intervention will receive support by an e-coach. They can contact their e-coach in case of questions or if they wish to get feedback for any of their completed modules. E-coaches are trained and supervised psychologists (by HB, AMK) psychologists that give semi-standardized feedback after participants finish their modules within two working days, following an e-coach manual. Whenever participants have questions or wish to get feedback on their module input, they can contact their personal e-coach via the Minddistrict' platform's message function. At the beginning of the intervention, each participant receives a welcoming message in which their e-coach introduces himself. Additionally, the first module explicitly highlights the possibility to contact the e-coach at any time. The feedback content is specific to the participants' assignments in order to support treatment adherence. It also includes positive reinforcement to encourage and motivate the participants to continue the intervention. E-coaches are instructed to document any responses to questions or give feedback. This will enable the evaluation of actual usage of a guided intervention by participants.

Control condition

Participants in the waitlist control group have unrestricted access to any usual treatment options. They receive an information leaflet informing them about alternative support options such as university counseling services, psychotherapy or helplines as well as the advice to seek help in case their well-being declines. Six months after randomization, participants of the control condition receive the unguided version of the intervention.

Assessments and outcomes

Assessments take place before (t0; pre-measurement) as well as after eight weeks (t1; post measurement) and six months (t2; follow-up) after randomization. All self-report data are collected using the online survey platform "Unipark" (www.unipark.de). Further, participants have to come to the laboratory of the department Clinical and Health Psychology to collect the psychobiological data (heartbeat perception task, hair samples for cortisol and DHEA as well as buccal cell swabs for the collection of DNA from buccal mucosa for genotyping FKBP5).

Biological samples are processed in the Department of Clinical & Biological Psychology directly under the supervision of AK. Participants receive 20 EUR or 3 course credits compensation for the laboratory assessment. Importantly, they do not obtain any compensation for participation in the intervention.

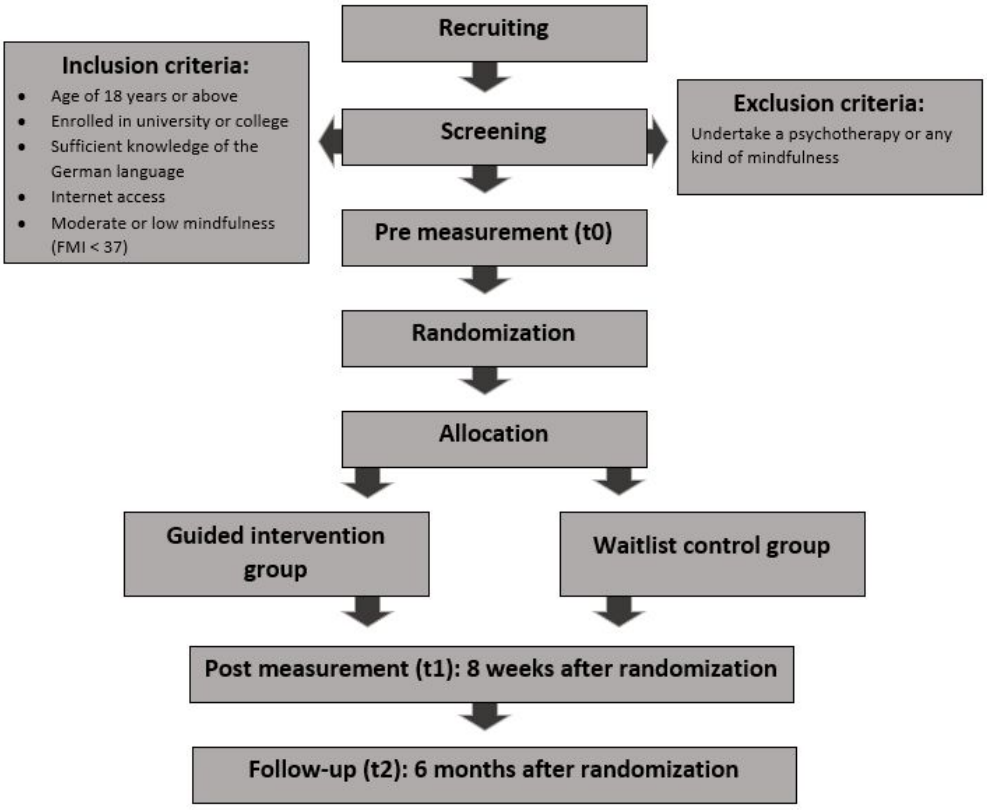

Figure 1. Flow chart of the study design

Primary outcome: Mindfulness

The 14-item short scale of the Freiburg Mindfulness Inventory (FMI) [103, 107] is used to derive a mindfulness score. The FMI consists of a 4-point Likert scale ranging from 1 = “rarely” to 4 = “almost always”. The short scale is sensitive to changes and appropriate for investigating subjects without meditation experience [103]. In a study by Heidenreich, Ströhle, and Michalak [108], a high internal consistency with a Cronbach’s Alpha of 0.84 could be shown.

Secondary outcomes

Depressive symptoms. The depression module of the Patient Health Questionnaire (PHQ-9) [109] comprises nine items that are rated on a 4-point Likert scale (0 = “not at all” to 3 = “nearly every day”). The PHQ-9 is a widely used depression screening that has been demonstrated to be a valid instrument with good diagnostic properties (sensitivity of 0.95 and specificity of 0.84) and internal consistency (α = .89) [110].

Anxiety. The Generalized Anxiety Disorder Questionnaire (GAD-7) [111] consists of a 7-item anxiety scale ranging from “not at all” (= 0) to “nearly every day” (= 3) and is used to screen for generalized anxiety disorder. Evaluations of the questionnaire showed a sensitivity of 0.89, specificity of 0.82 and a good test-retest reliability (intraclass correlation = .83). The GAD-7 has been identified as a reliable and valid measure of anxiety in the general population with Cronbach's alpha of .89 [112].

Stress. The Short Form Perceived Stress Scale (PSS-4), derived from the Perceived Stress Scale [113], is used to measure the participant’s perceived stress as the degree to which situations in one’s life are rated as stressful (scale ranging from 0 = “never”, 4 = “very often”). The psychometric properties of the PSS-4 are acceptable and reliable across cultures, with Cronbach’s alpha of .77 [114].

Well-being. The well-established 5-item World Health Organization Well-Being Index (WHO-5) [115] is used to assess subjective psychological well-being. The response scale referring to the frequency of relevant feelings over the past two weeks ranges from “*at no time*” (= *0*) to “*all of the time*” (= *5*). With a sensitivity of 0.86 and specificity of 0.81, WHO-5 is a screening tool for depression, which has been demonstrated among several clinical studies. Applicability across study fields and clinical validity have been identified as very high [116].

Interoceptive sensibility. Interoceptive sensibility (IS) is assessed by the awareness section of the Body Perception Questionnaire (BPQ) [117]. It includes 45 items of individual identifications of bodily signals on a 5-point Likert scale, ranging from “never” (= 1) to “always” (= 5). Calculated t scores reflect a standardized value according to a normal distribution based on a mean of 50 and a standard deviation of 10. Previous reports for the reliability exist only for the short form of the Body Perception Questionnaire [118], showing a categorical omega coefficient between .68 and .97. Moreover, high retest reliability could also be approved.

Emotion regulation. A German translation [119] of the Emotion Regulation Questionnaire (ERQ) [120] is used to assess individual differences in the habitual use of two emotion regulation strategies, reappraisal, and suppression. The questionnaire includes six items measuring reappraisal and four items measuring suppression. Participants are required to indicate whether they agree with each statement on a 7-point Likert scale ranging from 1 (= “strongly disagree”) to 7 (= “strongly agree”). The ERQ demonstrates good scale score reliability for the suppression (Cronbach's alpha = .76) as well for the reappraisal factors (Cronbach's alpha = .74) [119].

Alexithymia. The Toronto-Alexithymia Scale (TAS-20) [121]; German adaptation by Kupfer et al. [122]) measures alexithymia. The questionnaire consists of 20 items rated on a five-point Likert scale (1 = “strongly disagree”; 5 = “strongly agree”) with total scores ranging from 20 to

100, reflecting three-factor scales: “difficulties identifying feelings” (DIF), “difficulty describing feelings” (DDF) and “externally oriented thinking” (EOF). Higher scores on the different subscales indicate higher levels of alexithymia. The TAS-20 is a valid instrument with good internal consistency (Cronbach’s alpha of 0.85 to 0.86) and test-retest reliability [123].

Subjective side effects and adverse events. In a survey with 195 former psychotherapy patients, 94 % stated to have experienced negative effects during or after psychotherapy [124]. Consequently, Ladwig and co-workers [124] developed the Inventory for the Assessment of Negative Effects (INEP), which is included to assess any changes experienced during or after the treatment in the social and/or work environment and whether they are attributed to the psychotherapeutic intervention. The items cover potential adverse events in the personal, intrapersonal and social context (e. g. “emotions”, “family and friends”). Four items are rated on a 7-point bipolar scale (-2 = “worse”, +3 = “better”), the others are rated on a four-point scale (0 = “no agreement”, 3 = “full agreement”). The present trial an adapted 22-item version covering possible negative effects associated specifically with online-trainings (e.g., concerns about data protection) is applied. The original scale has demonstrated high internal consistency with a Cronbach’s alpha of 0.86 [124].

Intervention satisfaction and adherence. The Client Satisfaction Questionnaire (CSQ) [125] is a validated 8-item tool and is used in a German version adapted for the evaluation of IMIs (ZUF-8) [126]. The CSQ-8 comprises eight items, each with a 4-point scale of specific response alternatives (e. g. 1 = “quite unsatisfied”, 4 = “very satisfied”). Good psychometric properties have been demonstrated including Cronbach’s alphas between .88 and .92 [127]. Additionally, qualitative feedback is assessed via a self-developed questionnaire for further optimization of the intervention. Adherence is operationalized by the number of modules participants complete during the “per protocol” intervention period of eight weeks.

Psychobiological outcomes

Besides the assessment of different self-reported health variables, we also assess psychobiological variables. These include the assessment of the heartbeat perception task (= interoceptive accuracy) as well as hair cortisol and DHEA at all three measurement points. The FKBP5 genotype dichotomous model (CC vs. CT/TT carriers) is only assessed at the pre-measurement and is used as a covariate in the analyses.

Heartbeat perception task. The heartbeat perception task by Schandry [128] assesses the sensitivity for cardiovascular signals, namely interoceptive accuracy. Therefore, participants are instructed to listen to their own heartbeats and count them silently during four different intervals. For the present study, we chose a training interval of 15 seconds to get familiar with

the task, followed by four test intervals (35, 45, 25 and 60 seconds). Importantly, participants do not get any information about the length of these intervals. They receive start and stop signals for each interval from the investigator. After every stop, they have to report their counted heartbeats as well as their confidence ratings regarding them (1 = "total guess/no heartbeat awareness" to 10 = "complete confidence/full perception of heartbeat"). Biopac MP 150 (sampling rate 1000 Hz) is used for recording.

Hair cortisol and DHEA. To assess the changes in the psychophysiology stress level across the time of intervention, cortisol and DHEA are used. Therefore, two strains (~ 3 mm diameter) with a length of minimum 2 cm are obtained from the posterior vertex of each participant. Importantly, hair should be cut as close to the scalp as possible, using a fine medical scissor. The scalp hair is wrapped in aluminum foil and stored at -20°C in a dry, dark place until the analyses start.

Gene FKBP5. For the investigation of a possible gen x environment interaction, the FKBP5 genotype is included as another psychobiological variable in the study. Therefore, samples from the buccal mucosa are taken non-invasively using buccal mucosa collection swabs (Salimetrics, UK). DNA from buccal cells is isolated using commercially-available column-based purification techniques (Qiagen, Germany). DNA is tested for quality (260/280 nm absorption) and concentration (Qubit, Thermofisher, USA). TaqMan assays for FKBP5 genotyping at position rs1360780 (T/C-allele) are performed using qPCR technology on a QuantStudio6 machine (Thermofisher, USA).

Covariates. To investigate potential effect-modifying influences [129], several sociodemographic variables are assessed: age, gender, nationality, marital status, study course and number of semesters, weight and height (= BMI), previous experience with mindfulness, time spent practicing mindfulness, psychotherapy experience and use of additional treatment options (such as psychological counselling or psychotherapy). Regarding the hair analyses, we evaluate current hair color and coloring, hair structure and existence of permanent waves. To examine the influence of treatment expectations on outcomes the Client Expectancy Questionnaire is used, which has demonstrated high internal consistency (α = 0.84-0.85; CEQ) [130]. It consists of six items which are measured on a 9-point Likert Scale with higher scores representing positive expectations and credibility. Additionally, we collect data in the post-measurement of the online survey regarding the claim of other support (coaching, psychotherapy, psychiatry, family doctor, psychotropic drugs, mindfulness training, other health training or "StudiCare" projects). Further, if subjects participate in another kind of mindfulness training, they are asked to report how it works (presence, online, book, coaching).

Table 2. Summary of the outcome assessments and assessment time points

Variables	Measurement	Screening	T0	T1	T2
Inclusion and exclusion criteria					
Demographic variables	E.g., age, enrolled in a university, internet access, mindfulness intervention	X			
Short scale of the Freiburg Mindfulness Inventory	Mindfulness	X			
Primary Outcome					
Short scale of the Freiburg Mindfulness Inventory	Mindfulness		X	X	X
Secondary Outcome					
Patient Health Questionnaire	Depression		X	X	X
Generalized Anxiety Disorder Questionnaire	Anxiety		X	X	X
Short Form Perceived Stress Scale	Stress		X	X	X
World Health Organization Well-Being Index	Well-being		X	X	X
Body Perception Questionnaire	Interoceptive Sensibility		X	X	X
Emotion Regulation Questionnaire	Reappraisal and suppression		X	X	X
Toronto Alexithymia Scale	Alexithymia		X	X	X
Heartbeat perception task	Interoceptive Accuracy		X	X	X
Cortisol & DHEA	Psychobiological stress level		X	X	X
Covariates					
Demographic variables	E.g., weight, height, psychotherapy		X		
Previous experience with mindfulness, time spent practicing mindfulness and use of additional treatment options	Self-reported mindfulness and treatment experience		X	X	X
Genotype FKBP5 (rs1360780)	Gen x environment interaction		X		
Client Expectancy Questionnaire	Treatment expectancy and rationale credibility		X		
Dropout	Intervention adherence		X	X	
Client Satisfaction Questionnaire	Intervention satisfaction			X*	
Inventory for the Assessment of Negative Effects	Potential adverse effect			X*	

Note. * only for the intervention group

Sample size estimation

The sample size estimation based on a calculation of G*Power 3.1.9.2, assuming a small effect size of f = .15 (consistent with d = .3) in a repeated measurement model and a comparison of two groups. Based on an α-level of .05 and power of .90, the total sample should consist of 120 participants including 60 for the guided intervention group and 60 for the waitlist control group. The assumed effect size of d = .3 is based on the meta-analysis of Jayewardene, Lohrmann et al. [65] and Spijkerman et al. [64] regarding online mindfulness-based interventions.

Ethics and dissemination

All study procedures were approved by the ethics committee of Ulm University (application No. 48/18). The trial was registered prior to the recruitment at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register (DRKS; ID: DRKS00014701). Participants receive written information on study conditions, data security, voluntariness of participation and the right to leave the study at any time. To confirm understanding, written consent is obtained from all participants prior to study entry. Data collection are pseudonymized and are only accessed by authorized study personnel obliged to secrecy. The results will be published in peer-reviewed journals and presented on international conferences.

Statistical analyses

All statistical analyses will be conducted according to the Intention-To-Treat (ITT) principle. Procedures of imputation will be chosen based on patterns and mechanism of missingness (e. g. by multiple imputations). Additionally, per protocol analyses will be performed to examine the impact of dropouts on study results. The significance level for all analyses will be $p \leq .05$.

Standardized mean differences with 95% confidence intervals will be calculated post-treatment and follow-up to analyze between-group effect sizes. Regression analyses will be performed as a primary method, using linear regression for dichotomous outcomes. Based on the data structure, regression analysis will be adjusted accordingly (e.g., use of robust estimation or use of multilevel regression analysis in case of substantial intra-class correlation). Analyzed variables will include the covariates (e.g., age, gender, gene FKBP5) using path modeling.

Discussion

This study protocol describes the study design of a randomized controlled trial that investigates psychobiological health-related variables additional to the commonly used self-report data of a guided online mindfulness-based intervention in a student sample. We assume that individuals who participate in the guided intervention show decreased depression, anxiety and stress levels as well as reduced alexithymia in comparison to the waitlist control group.

Furthermore, we suppose an increase of well-being, interoceptive sensibility and emotion regulation in the intervention group. Focusing on different psychobiological variables (interoceptive accuracy, hair cortisol, and DHEA) we expect similar positive effects. In order to find out more about the covariates, we also include sociodemographic data, the gene FKBP5, and expectations regarding the intervention in our analyses.

Our study focuses on some aspects discussed in previous studies, aiming at combining these points here. Consequently, this study has several strengths:

(1) *Combination of self-report and psychobiological measurements*

In comparison to earlier studies, our investigation includes self-report and psychobiological markers. Consequently, we use subjective as well as objective parameters to emphasize our results, meaning that especially psychobiological markers are less biased compared to the self-report measurements. Nonetheless, research so far showed that a combination of both is suitable to include advantages and disadvantage of both approaches [66, 67, 131]. Furthermore, the hair stress markers represent longitudinal markers from the last weeks or even months [79]. In contrast, cortisol measurements such as salivary, plasma or urine are time-limited and depend on changes associated with circadian rhythm regulation.

(2) *Procedures to improve the adherence level*

Our interventions include different opportunities to improve adherence. This is almost based on the high dropout rates of 40 to 70 percent in different online or smartphone interventions [60, 132, 133]. Firstly, we only include participants with low or moderate mindfulness in our intervention. One reason for choosing this level is a potential higher motivation and interest, resulting in an assumed lower dropout rate in the intervention. However, it should be mention that it is only a hypothesis, which is not measured in the study. Secondly, we use different modes of delivery in order to increase the adherence level of our online intervention. These include text, audio files, self-reflection, homework, instructions, and tips for implementing and transferring intervention components into daily life. Following the main seven intervention modules, participants also get two booster sessions, which summarize and repeat the other modules before. Thus, a long-term effect is supposed to be obtained, and the adherence level is expected to be high. Thirdly and importantly, we include e-coaching in our training. A current study of Kvillemo and co-workers [60], report that a higher contact level decreases the dropout rate and is an important option that increases the adherence level of participants. The e-coach has the task to give the participants feedback concerning the completed modules and remind them if they do not attend. Additionally, participants get the opportunity to contact the e-coach via the messenger system of Minddistrict. Lastly, the online mindfulness-based

intervention is tailored to the particular need of a student sample. This is another point to raise the adherence level and likely to enhance the effectiveness of the online intervention.

(3) *Adherence level*

To find out more about the reasons for different adherence levels, participants also have to answer quantitative and qualitative questions regarding the content of modules and their motivation. These responses will help us to adapt and improve the online intervention and accordingly enhance adherence.

(4) *Follow-up measurements six months after randomization*

Several studies represent that no follow-up measurements have been implemented [e.g., 60, 62, 63, 134]. Other studies used different intervals for the follow-up measurement after the intervention, ranging from two weeks up to six months [e.g., 29, 44, 61, 132, 135]. To focus on the longitudinal effects of our intervention, we examine participants again six months after randomization.

Assuming positive results of the present online mindfulness-based intervention, it could be a helpful opportunity for universities to establish such time and cost-effective healthcare services. Given the high stress rate in the student population, the present intervention will contribute information and practices to decrease individual's stress levels as well as to improve mental health in general. Another advantage is the prevention of other upcoming mental health problems, resulting from a high stress level. Thus, this stand-alone intervention can provide advantages for users and the health care system. Moreover, results will have implications for researchers, health care providers and public health policymakers.

Authors' contributions

DS, AMK, DDE, HB, and OP initiated this study. DS, AMK, AK, HB, and OP contributed to the design of this study. DS, AMK, CS, and FW adapted the intervention content and the assessment. DS and CS are responsible for recruitment. AK performed FKP5 genotyping and provided a methodology for the collection of hair and sample preparation for steroid analysis. He supervised all stages of biological assessments and analyses. DS wrote the draft of the manuscript. All authors contributed to the further writing of the manuscript and approved the final version of the manuscript.

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Competing interests statement

DS, AMK, DDE, HB, and OP were involved in the development of "StudiCare Mindfulness" or its predecessor versions. HB reports having received consultancy fees and fees for lectures/workshops from chambers of psychotherapists and training institutes for psychotherapists in the e-mental-health context. DDE reports having received consultancy fees/served in the scientific advisory board from several companies such as Minddistrict, Lantern, Schoen Kliniken and German health insurance companies. He is a stakeholder of the Institute for health training online (GET.ON), which aims to implement scientific findings related to digital health interventions into routine care.

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Effectiveness of a guided online mindfulness-focused intervention in a student population: Study protocol for a randomized control trial

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Abstract

Background: Previous studies show that university students experience higher psychological stress than the general population, resulting in increased vulnerability for mental disorders for the student population. Online mindfulness interventions will be delivered to students as a potentially promising and more flexible approach compared to face to face intervention with the aim of improving their mental health. This study purposes to investigate the effectiveness of a guided online mindfulness-focused intervention for university students by using both self-reported and psychobiological measures.

Methods and analyses: In this multicenter, two-armed randomized controlled trial (RCT) with a parallel design, a guided version of the online mindfulness-focused intervention "StudiCare Mindfulness" will be compared to a waitlist control group. In total, 120 participants will be recruited at different universities (of Applied Sciences) in (Neu-) Ulm. Data will be assessed prior to randomization, after eight weeks (post-intervention) and six months after randomization (follow-up). The primary outcome measure is mindfulness. The secondary outcome measures include depression-, anxiety- and stress level, well-being, interoceptive sensibility, emotion regulation and alexithymia. Psychobiological parameters comprise interoceptive accuracy, hair cortisol, and FKBP5 genotype. Sociodemographic variables, treatment expectations, side, and adverse side effects, as well as intervention satisfaction and adherence will be assessed. All data analyses will be conducted according to the Intention-To-Treat (ITT) principle.

Ethics and dissemination: All study procedures have been approved by the ethics committee of Ulm University (application No. 48/18). The findings will be disseminated widely through peer-reviewed publications and conference presentations.

Trial registration: The trial is registered at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register: DRKS00014701 (registration date: 07th May 2018; URL: https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00014701). In case of important protocol modifications, trial registration will be updated.

Keywords: RCT, eHealth, online intervention, stress, mindfulness, effectiveness, psychobiological measures

Strengths and limitations of this study

- "StudiCare Mindfulness" is an online mindfulness-focused intervention program with the aim to increase mindfulness and simultaneously decrease stress level in order to reduce mental disorders in university students.

- This study considers psychobiological parameters in addition to the common participants´ self-report data prior to randomization as well as eight weeks and six months after randomization.
- A follow-up measurement six months after randomization is administered.
- Because of the use of psychobiological parameters, the study will only be conducted at universities (of Applied Sciences) in (Neu-) Ulm, which could reduce generalizability.

Background

Stress is highly prevalent among university students. Previous studies showed that compared to the general population, students have significantly higher stress levels [1–3]. The increased clinical levels of stress in university students has been linked to a range of stressors such as new experiences and challenges in addition to new social relationships, academic pressures and exams [2, 4–7]. Moreover, such high stress levels have the potential to trigger a new mental illness such as anxiety and/or depression or exacerbate a pre-existing mental health condition [8–14]. For example, Auerbach and co-workers [15] found in an international WHO-survey that more than 20 percent of university students reported a mental disorder. However, it should be noted that 83 percent of these students had a mental illness onset before commencing their studies. Similar results were found in another survey, indicating that 23 percent of the university students met the criteria for a mental disorder [16]. The development of a mental disorder is related to a more severe and chronic disease trajectory, a higher risk to develop comorbidities, decreased academic performance, as well as an increased probability for dropouts during the university career [5, 9, 17–19].

Accordingly, it is crucial to prevent elevated stress levels to reduce the risk of university students developing a mental health disorder. In this context, previous studies revealed that most university students do not use face-to-face interventions and do not seek professional help, although most of the universities provide free health and counseling services [8, 20–26]. Prohibitive factors to accessing services reproted by university students included: lack of time, fear of stigma, the preference to get help and support from family or friends as well as lack of knowledge regarding available services at the university. Thus, internet- and mobile-based psychological interventions (IMIs) may offer a promising approach to close the gap between these barriers and to provide additional advantages (e.g., no need of therapist availability, low-threshold access, stigma-reduction, cost-effectiveness as well as flexibility regarding time and place) [22, 23, 27–31]. Emerging evidence from different studies has also demonstrated that online interventions can be as effective as face-to-face programs in healthy and clinical populations [32–34]. Furthermore and most importantly, nowadays young people grow up in a digital world and prefer using the internet as well as smartphones daily [35–37]. They are also searching for health information online [38]. However, a study with an Australian sample (mean age 36.6 years) showed that 77.1% prefer face-to-face intervention [39]. In another study by Ryan and colleagues [26], findings indicate that nearly 50% of university students (mean age 23.7) in Australia have a preference for online interventions. Consequently, the age range and the context seems to be crucial for understanding the preferences of the type of therapy delivery in students, [26].

Moreover, Stallman and Kavanagh [40] as well as Ebert and co-workers [27], observed that university students show a high acceptance and usability for online interventions. A growing body of research found that online interventions are helpful to improve mental health conditions [27, 41–46]. These effects can be enhanced by therapeutic guidance, meaning that additionally participants receive support from an expert, either online or face-to-face whilst receiving their online intervention [6, 47].

One opportunity to improve mental and physical health is mindfulness. Mindfulness is the awareness of the present moment in an open, accepting and non-judgmental way with the focus on internal bodily signals (e.g., ones' breathing and other bodily sensations [48–50]) as well as external stimuli (e.g., sounds, pictures, behavior [51]) . Several studies found positive effects of a mindfulness-based intervention on mental and physical health conditions, independent of whether these included healthy or clinical participants [52–60]. Furthermore, Wahbeh and colleagues [60] found in their study sample that there was a preference for online mindfulness-based interventions compared to group or one-by-one interventions. As there are clear benefits of mindfulness based interventions as well as as online interventions such as e-health programs, it seems timely to combine these approaches to reduce stress and therefore to improve mental health in a student population.

Numerous studies [44, 61–64] and meta-analyses [65, 66] found evidence for the efficacy of online mindfulness-based interventions with the focus on self-reported health variables (e.g., depression, anxiety, and stress). For example, Spijkerman, Pots and Bohlmeijer [65] compared 15 randomized control trials and showed small to medium effect sizes regarding the reduction of anxiety (g = .22; 95% CI: .05 - .39), improvement of depression (g = .29, 95% CI: .13 - .46), well-being (g = .23; 95% CI .09 - .38) and mindfulness (g = .32, 95% CI .23 - 42) in healthy samples as well as samples with mental disorders. Especially for stress reduction a large effect was shown (g = .51; 95% CI: .26 - .75). Similar results were found in another meta-analysis conducted by Jayewardene, Lohrmann, Erbe, and Torabi [66]. The authors compared eight studies focusing on the effects of online mindfulness interventions in populations with subclinical mental health conditions in non-clinical populations (g = .28 - .42; 95% CI: .15 - .67). Moreover, these results showed further improvements in mental health at follow-up (g = .47 - .70; CI: .14 - 1.13). Even though these findings are promising, self-report data might substantially overestimate the effectiveness of interventions. Hence, the field should move forward to include more objective data, to verify the promising results, by including assessments of psychobiological variables.

Until now, there are no studies regarding the effectiveness of online mindfulness-focused training on psychobiological variables, which represent objective markers of mental health conditions. Such variables are not influenced by social desirability, memory problems or a

conscious perception [67]. Consequently, psychobiological data provide additional markers to complement the self-reported data and should, therefore, be included in mindfulness and stress-related intervention studies. In this study, we will include psychobiological measurements of interoceptive accuracy as well as cortisol and dehydroepiandrosterone (DHEA). Interoceptive accuracy represents the behavioral assessment of an individual's ability to perceive internal bodily changes, which is mostly assessed via the heartbeat perception task [68]. Moreover, interoceptive accuracy is associated with other health-related variables such as emotion perception and regulation, alexithymia, stress, depression, anxiety symptoms, and eating behavior [69–74] and can be influenced by the mentioned health-related variables. Recent studies focusing on interoceptive accuracy have shown mixed results regarding the impact of different offline mindfulness interventions [75–77].

Two biological indicators of the body's physiological stress response are cortisol and DHEA. While cortisol is a steroid hormone released by the hypothalamic-pituitary-adrenalin (HPA) axis in response to stress [78], DHEA represent an endogenous steroid hormone on the stress response that can antagonize the effect of cortisol [79]. To assess long-term effects of stress, collecting hair samples is superior to fluid biomaterial (e.g., saliva, blood), because hair samples reflect the stress level of weeks or even months and are not influenced by acute stress before or during the measurements or body's circadian rhythm as well as hormone level [80–83]. Accordingly, the ratio between cortisol and DHEA seems to be important. There is only one study showing positive effect of a 8-week body scan training (one approach of the mindfulness-based stress reduction program) on cortisol, DHEA and the ration [84]. Several other studies reveal inconsistent results concerning the effect of mindfulness interventions on stress parameters assessed by saliva or plasma cortisol [85–90]. Moreover, there is no other evidence in previous research of mindfulness training on DHEA. However, some studies measured the sulfated form of DHEA (DHEA-S) and found no effect on DHEA-S after an 8-week mindfulness-based stress program in a population diagnosed with cancer. To combine both stress markers, different researchers suggest the cortisol/DHEA ratio as a parameter for the endocrine imbalance of HPA regulation [91–95]. Comparable with DHEA, there is only one study that has investigated the cortisol/DHEA-S ratio. It indicated that men diagnosed HIV-positive had an improved ratio after participating in a cognitive-behavioral stress management program in comparison to a waitlist control group [94]. To sum up, studies examining psychobiological parameters in mindfulness-based programs are very sparse, though there are some promising results. Nonetheless, such investigations are essential to characterize the long-term effects of mindfulness on psychobiological processes.

Another interesting marker is the gene FKBP5 coding for FK506 binding protein 51 (FKBP51). FKBP51 is a co-chaperone of the glucocorticoid receptor, changing its affinity for cortisol and therefore influencing the reactivity of cortisol-mediated stress signaling in

the body. Compared to C-allele carriers (wild type) at position rs1360780, individuals with the T-allele show a higher risk for depression and less clinical responsiveness to antidepressant treatment [96]. Also, T-allele carriers show more pronounced changes in hair cortisol levels with increasing childhood maltreatment compared to C-allele carriers, demonstrating a gen x environment interaction with a dose-response relationship between adverse childhood experiences, a strong predictor for late-life depression, and steroid hormones of the body's stress response [97]. In comparison to the other psychobiological stress marker, FKBP5 can only be assessed once, because there is no fluctuation. Consequently, this marker will be included as a covariate variable.

An additional focus of the present trial is the effectiveness of guidance during the online mindfulness-focused intervention. Research in this context provides evidence that guided online intervention enhances the efficacy of health-related variables [65, 98]. In the context of online mindfulness training for students, only the study of Mak and colleagues [62] provided telephone or email support without a control group.

Taken together, we hypothesize that

1) The primary outcome mindfulness will be improved after the intervention in comparison to a waitlist control group.
2) The secondary outcomes of depression, anxiety, stress level, interoceptive sensibility, emotion regulation, and alexithymia will also be improved. We assume similar results for the psychobiological variables (secondary outcomes), including interoceptive accuracy (assessed via the heartbeat perception task) as well as cortisol and DHEA levels in hair.

Further, it should be noted that outcomes can be influenced by various covariates. For example, interoceptive accuracy can be influenced by emotion regulation, alexithymia or depression and anxiety symptoms [69, 72–74]). Therefore, we will test for potential effect-modifying variables on an exploratory level. Lastly, we intend to explore and analyze the participants' satisfaction, adherence and acceptance of the intervention.

Methods

Study design

This project is a two-armed randomized controlled trial with a parallel design comparing the effectiveness of a guided version of the online, preventive mindfulness intervention "StudiCare Mindfulness" to a waitlist control group (see Fig. 1 for flowchart). The research aims to examine the effectiveness of StudiCare Mindfulness on different self-reported and psychobiological health-related parameters at three measurement points (before the intervention as well as eight weeks and six months after randomization). Moreover, the individuals' adherence,

acceptance, and satisfaction are measured to identify possibilities to improve the intervention. Participants of both the control and the intervention group have access to treatment as usual. Thus, participants can use other support or treatment options that will be monitored in order to control for potential confounding effects.

The project takes part in collaboration with the Department for Clinical Psychology and Psychotherapy of Ulm University as one of two parallel mindfulness trials with a second trial investigating the effectiveness of a "guidance on demand" and an unguided version of "StudiCare Mindfulness" in comparison to a waitlist control group [99].

The present study is conducted and will be reported according to the CONSORT 2010 Statement [100] and the guidelines for executing and reporting internet intervention research [101]. The study protocol complies with recommendations of the SPIRIT 2013 Checklist for clinical trial protocols [102].

The "StudiCare Mindfulness" trial is carried out as part of the "StudiCare" project funded by BARMER, a cooperation of the Universities of Erlangen-Nuremberg and Ulm. The overall project aims to improve college university students' well-being by evaluating their mental health in longitudinal panel surveys as well as developing and offering a broad assortment of internet-based interventions for psychological and behavioral issues (such as procrastination, exam anxiety, physical activity). It is embedded in the "World Mental Health Survey International College Student" project (WMH-ICS) [103] as well as the "Caring Universities" project [104].

Patient involvement

University students as target end users of StudiCare Mindfulness were involved in the development process of the intervention. They will also be involved in the conduct and the reporting of the research, however, not in their role as end user but in their role as scientists. The public will be informed about the results on several ways, amongst others publications, lectures and workshops.

Eligibility criteria

Participants providing written informed consent as well as fulfilling the following inclusion criteria for participation will be applied: a) age of 18 or above, b) enrolled at Universities (of Applied Sciences) in Ulm or Neu-Ulm, c) sufficient knowledge of the German language, d) internet access, e) moderate to low mindfulness (Freiburg Mindfulness Inventory FMI < 37); this cut-off was chosen as it represents the medium value of the FMI in subjects from the

general population [105]. Participants are excluded from the study if they currently undertake psychotherapy or any mindfulness intervention. To investigate if participants are eligible, they have to fill out a screening questionnaire.

Setting/Recruitment

Recruitment has started in May 2018 and will continue until the target sample size of 120 participants will be reached. Participants are recruited from particular different universities in (Neu-) Ulm, including Ulm University, Ulm University of Applied Sciences and Neu-Ulm University of Applied Sciences because psychobiological parameters have to be assessed on-site. The following recruiting channels are used: email, flyer and poster, social media, student unions, and student counseling services. University students get information about the "StudiCare" offers and a link to the homepage (www.studicare.com), where they can get further information and register for the IMIs. Once registered, they receive an email with a link to the screening questionnaire. Depending on the location of their University, participants are either allocated to Kuechler et al.'s trial [99] (all other cooperating universities in Germany, Austria and Switzerland) or to the present study (students from different universities (of Applied Sciences) in Ulm and Neu-Ulm), as psychobiological tests demand actual attendance on-site). Once the screening is completed, participants receive an email with further information on the study as well as an informed consent form, which they are required to send back to the study staff via email. When written consent is obtained and the pretest completed, another email is sent to inform participants about their group (intervention or waitlist control group). If participants are part of the intervention group, they will also receive a link to the intervention. Participants are informed that "StudiCare Mindfulness" cannot replace psychotherapy and are recommended to seek counseling/psychotherapy in case of distinctive mental health problems. Additionally, they are provided with alternative treatment options and contact details (this information is also given to participants who do not meet the selection criteria).

Randomization

After completing the baseline assessment, participants are randomly allocated to one of two study groups (guided vs. waitlist control group) by an independent member of the Ulm University not otherwise involved and therefore blinded to all processes of the study. Via an automated, online-based randomization program (www.sealedenvelope.com), permuted block randomization is performed with an allocation ratio of 1:1 and variable block sizes of 2 and 4 (randomly arranged).

Intervention

The online mindfulness-focused intervention consists of seven weekly, target-group-specific modules of approximately 60 min. each. Additionally, two booster sessions are activated four and twelve weeks after completion of the seventh module in order to enhance the sustainability

of intervention effects. These booster sessions include a summary of the seven previous modules. Our aim was to give participants the possibility to collect a repertoire of useful methods. Beyond that, already completed sessions are accessible and can be repeated as often as participants wish to. All modules contain information on stress, well-being, and mindfulness with a weekly alternating focus on different topics such as interoception, dysfunctional and beneficial thinking, values and goals. Whereas these contents are provided via texts, images and interactive elements (such as quizzes or conditional content), the focus of the intervention lies on the regular practice of mindfulness exercises such as body-scans, breathing meditations or mindful yoga. Therefore, each module includes downloadable audio files as well as mindfulness diaries to be completed in weekly homework assignments. At the beginning of each module, participants are encouraged to reflect on their assignments and also on their most and least mindful moments of the week. The content of the intervention is mainly based on Acceptance and Commitment Theory [106] as well as mindfulness-based stress reduction [107] and also includes some elements of stress management [108] and cognitive-behavioral therapy. We summarized the different methods as one mindfulness-focused intervention.

The intervention's primary goal is to increase the student participants' mindfulness and psychological flexibility in order to enable them to manage their daily hassles flexibly. Furthermore, the intervention was developed by the Department of Clinical Psychology and Psychotherapy, Ulm University. Its efficacy has already been demonstrated in a randomized controlled trial [109]. Based on participants' feedback the different sessions were adapted and further refined. Moreover, the two weekly sessions ("Mindfulness body perception" and "Body and sense") were also extended. Table 1 summarizes the topics and contents of each module. The intervention is available for participants on the Minddistrict platform (www.minddistrict.com), a company specialized in the provision of internet-based health interventions. Participants can get access to the platform via their personal username and password on a 24/7 basis. All transferred data will be secured based on ISO27001 and guidelines NEN7510.

Table 1. Overview of the different topics and contents of each module

Module	Aims and content	Examples of exercises and assignments
1. Being in the here and now	Introducing the concept of mindfulness	Reviewing most and least mindful moments of the day; practicing Body Scan; taking mindful walks
2. Mindful body perception	Practicing awareness of body signals	Testing one's heartbeat perception; practicing "heart meditation"; mindful eating and drinking
3. A new perspective on stress	Distancing oneself from stress-inducing thoughts	Identifying former ways of coping with stress; learning techniques to challenge automatic thoughts; meditation exercise
4. Developing beneficial thoughts	Getting to know alternative ways of thinking	Identifying one's "stress patterns" and developing and internalizing beneficial thoughts; practicing breathing meditation
5. What makes your life valuable?	Identifying one's values and pursuing one's goals	Writing a speech for one's 70th birthday; setting and pursuing goals with the SMART technique; meditation exercise
6. Being mindful towards yourself	Learning how to accept one's personality traits appreciatively	Exercise to identify different personality traits and corresponding automatic reactions; learning to accept and appreciate all personality traits
7. Training your body and senses	Exercising the ability to enjoy and getting acquainted with the practice of yoga	Mindful chocolate eating exercise; mindful yoga exercises
Booster-Session 1 (4 weeks after completion of module 7)	Repeating module 1 to 3 and mindfulness exercises	Choosing favorite mindfulness exercises; setting goals for their implementation in the coming weeks
Booster- Session 2 (12 weeks after completion of module 7)	Repeating modules 4 to 7 and ensuring long-term integration of mindfulness into daily life	Reviewing pursuit of goals in the last two months; identifying potential barriers and developing solutions

Guidance and promotion of adherence

Participants randomized to the intervention will receive support by an e-coach. They can contact their e-coach in case of questions or if they wish to get feedback for any of their completed modules. E-coaches are trained and supervised psychologists (by HB, AMK) psychologists that give semi-standardized feedback after participants finish their modules within two working days, following an e-coach manual. Whenever participants have questions or wish to get feedback on their module input, they can contact their personal e-coach via the Minddistrict' platform's message function. At the beginning of the intervention, each participant receives a welcoming message in which their e-coach introduces himself. Additionally, the first module explicitly highlights the possibility to contact the e-coach at any time. The feedback content is specific to the participants' assignments in order to support treatment adherence. It also includes positive reinforcement to encourage and motivate the participants to continue the intervention. E-coaches are instructed to document any responses to questions or give

feedback. This will enable the evaluation of actual usage of a guided intervention by participants.

Control condition

Participants in the waitlist control group have unrestricted access to any usual treatment options. They receive an information leaflet informing them about alternative support options such as university counseling services, psychotherapy or helplines as well as the advice to seek help in case their well-being declines. Six months after randomization, participants of the control condition receive the unguided version of the intervention.

Assessments and outcomes

Assessments take place before (t0; pre-measurement) as well as after eight weeks (t1; post measurement) and six months (t2; follow-up) after randomization. All self-report data are collected using the online survey platform "Unipark" (www.unipark.de). Furthermore, participants come to the laboratory of the department Clinical and Health Psychology to collect the psychobiological data (heartbeat perception task, hair samples for cortisol and DHEA as well as buccal cell swabs for the collection of DNA from buccal mucosa for genotyping FKBP5). Biological samples are processed in the Department of Clinical & Biological Psychology directly under the supervision of AK. To get an overview of the different outcome measures and assessement time points see table 2. Participants receive 20 EUR or 3 course credits compensation for the laboratory assessment. Importantly, they do not obtain any compensation for participation in the intervention.

*** Please insert Figure 1 here ***

Primary outcome: Mindfulness

The 14-item short scale of the Freiburg Mindfulness Inventory (FMI) [105, 110] is used to derive a mindfulness score. The FMI consists of a 4-point Likert scale ranging from 1 = "rarely" to 4 = "almost always". The short scale is sensitive to changes and appropriate for investigating subjects without meditation experience [105]. In a study by Heidenreich, Ströhle, and Michalak [111], a high internal consistency with a Cronbach's Alpha of 0.84 was shown.

Secondary outcomes

Depressive symptoms. The depression module of the Patient Health Questionnaire (PHQ-9) [112] comprises nine items that are rated on a 4-point Likert scale (0 = “not at all” to 3 = “nearly every day”). The PHQ-9 is a widely used depression screening that has demonstrated validity and good diagnostic properties (sensitivity of 0.95 and specificity of 0.84) and internal consistency (α = .89) [113].

Anxiety. The Generalized Anxiety Disorder Questionnaire (GAD-7) [114] consists of a 7-item anxiety scale ranging from “not at all” (= 0) to “nearly every day” (= 3) and is used to screen for generalized anxiety disorder. Evaluations of the questionnaire show a sensitivity of 0.89, specificity of 0.82 and a good test-retest reliability (intraclass correlation = .83). The GAD-7 has been identified as a reliable and valid measure of anxiety in the general population with Cronbach's alpha of .89 [115].

Stress. The Short Form Perceived Stress Scale (PSS-4), derived from the Perceived Stress Scale [116], is used to measure the participant’s perceived stress as the degree to which situations in one’s life are rated as stressful (scale ranging from 0 = “never”, 4 = “very often”). The psychometric properties of the PSS-4 are acceptable and reliable across cultures, with Cronbach’s alpha of .77 [117].

Well-being. The well-established 5-item World Health Organization Well-Being Index (WHO-5) [118] is used to assess subjective psychological well-being. The response scale refers to the frequency of relevant feelings over the past two weeks ranging from “*at no time*” (= *0*) to “*all of the time*” (= *5*). With a sensitivity of 0.86 and specificity of 0.81, WHO-5 is a screening tool for depression, which has been demonstrated among several clinical studies. Applicability across study fields and clinical validity is very high [119].

Interoceptive sensibility. Interoceptive sensibility (IS) is assessed by the awareness section of the Body Perception Questionnaire (BPQ) [120]. It includes 45 items of individual identifications of bodily signals on a 5-point Likert scale, ranging from “never” (= 1) to “always” (= 5). Calculated t scores reflect a standardized value according to a normal distribution based on a mean of 50 and a standard deviation of 10. Previous reliability reports exist only for the short form of the Body Perception Questionnaire [121], showing a categorical omega coefficient between .68 and .97. and a high retest reliability.

Emotion regulation. A German translation [122] of the Emotion Regulation Questionnaire (ERQ) [123] is used to assess individual differences in the habitual use of two emotion regulation strategies, reappraisal and suppression. The questionnaire includes six items measuring reappraisal and four items measuring suppression. Participants are required to indicate whether they agree with each statement on a 7-point Likert scale ranging from 1 (=

"strongly disagree") to 7 (= "strongly agree"). The ERQ demonstrates good scale score reliability for the suppression (Cronbach's alpha = .76) as well for the reappraisal factors (Cronbach's alpha = .74) [122].

Alexithymia. The Toronto-Alexithymia Scale (TAS-20) [124]; German adaptation by Kupfer et al. [125]) measures alexithymia. The questionnaire consists of 20 items rated on a five-point Likert scale (1 = "strongly disagree"; 5 = "strongly agree") with total scores ranging from 20 to 100, reflecting three-factor scales: "difficulties identifying feelings" (DIF), "difficulty describing feelings" (DDF) and "externally oriented thinking" (EOF). Higher scores on the different subscales indicate higher levels of alexithymia. The TAS-20 is a valid instrument with good internal consistency (Cronbach's alpha of 0.85 to 0.86) and test-retest reliability [126].

Subjective side effects and adverse events. In a survey with 195 former psychotherapy patients, 94 % stated to have experienced negative effects during or after psychotherapy [127]. Consequently, Ladwig and co-workers [127] developed the Inventory for the Assessment of Negative Effects (INEP), which is included to assess any changes in the experiences during or after the treatment in the social and/or work environment and whether they are attributed to the psychotherapeutic intervention. The items cover potential adverse events in the personal, intrapersonal and social context (e. g. "emotions", "family and friends"). Four items are rated on a 7-point bipolar scale (-2 = "worse", +3 = "better"), the others are rated on a four-point scale (0 = "no agreement", 3 = "full agreement"). The present trial uses an adapted 22-item version covering possible negative effects associated specifically with online-training (e.g., concerns about data protection). The original scale has demonstrated high internal consistency with a Cronbach's alpha of 0.86 [127].

Intervention satisfaction and adherence. The Client Satisfaction Questionnaire (CSQ) [128] is a validated 8-item tool and is used in a German version adapted for the evaluation of IMIs (ZUF-8) [129]. The CSQ-8 comprises eight items, each with a 4-point scale of specific response alternatives (e. g. 1 = "quite unsatisfied", 4 = "very satisfied"). Good psychometric properties have been demonstrated including Cronbach's alphas between .88 and .92 [130]. Additionally, qualitative feedback is assessed via a self-developed questionnaire for further optimization of the intervention. Adherence is operationalized by the number of modules participants complete during the "per protocol" intervention period of eight weeks.

Psychobiological outcomes

We also assess psychobiological variables including the heartbeat perception task (= interoceptive accuracy) as well as hair cortisol and DHEA at all three measurement points. The

FKBP5 genotype dichotomous model (CC vs. CT/TT carriers) is only assessed at the pre-measurement and is used as a covariate in the analyses.

Heartbeat perception task. The heartbeat perception task by Schandry [131] assesses the sensitivity for cardiovascular signals, namely interoceptive accuracy. Therefore, participants are instructed to listen to their own heartbeats and count them silently during four different intervals. We chose a training interval of 15 seconds for participants to get familiar with the task, followed by four test intervals (35, 45, 25 and 60 seconds). Importantly, participants do not get any information about the length of these intervals. They receive start and stop signals for each interval from the investigator. After every stop, they have to report their counted heartbeats as well as their confidence ratings regarding them (1 = "total guess/no heartbeat awareness" to 10 = "complete confidence/full perception of heartbeat"). Biopac MP 150 (sampling rate 1000 Hz) is used for recording.

Hair cortisol and DHEA. To assess the changes in the psychophysiology stress level across the time of intervention, cortisol and DHEA are used. Therefore, two strains (~ 3 mm diameter) with a length of minimum 2 cm are obtained from the posterior vertex of each participant. Importantly, hair should be cut as close to the scalp as possible, using a fine medical scissor. The scalp hair is wrapped in aluminum foil and stored at -20°C in a dry, dark place until the analyses start.

Gene FKBP5. For the investigation of a possible gen x environment interaction, the FKBP5 genotype is included as another psychobiological variable in the study. Therefore, samples from the buccal mucosa are taken non-invasively using buccal mucosa collection swabs (Salimetrics, UK). DNA from buccal cells is isolated using commercially-available column-based purification techniques (Qiagen, Germany). DNA is tested for quality (260/280 nm absorption) and concentration (Qubit, Thermofisher, USA). TaqMan assays for FKBP5 genotyping at position rs1360780 (T/C-allele) are performed using qPCR technology on a QuantStudio6 machine (Thermofisher, USA).

Covariates. To investigate potential effect-modifying influences [132], several sociodemographic variables are assessed: age, gender, nationality, marital status, study course and number of semesters, weight and height (= BMI), previous experience with mindfulness, time spent practicing mindfulness, psychotherapy experience and use of additional treatment options (such as psychological counselling or psychotherapy). Regarding the hair analyses, we evaluate current hair color and coloring, hair structure and existence of permanent waves. To examine the influence of treatment expectations on outcomes the Client Expectancy Questionnaire is used, which has demonstrated high internal consistency (α = 0.84-0.85; CEQ) [133]. It consists of six items which are measured on a 9-point Likert Scale

with higher scores representing positive expectations and credibility. Additionally, we collect data in the post-measurement of the online survey regarding the claim of other support (coaching, psychotherapy, psychiatry, family doctor, psychotropic drugs, mindfulness training, other health training or "StudiCare" projects). Further, if subjects participate in another kind of mindfulness training, they are asked for the format (presence, online, book, coaching).

Table 2. Summary of the outcome assessments and assessment time points

Variables	Measurement	Screening	T0	T1	T2
Inclusion and exclusion criteria					
Demographic variables	E.g., age, enrolled in a university, internet access, current participation in mindfulness intervention	X			
Short scale of the Freiburg Mindfulness Inventory	Mindfulness	X			
Primary Outcome					
Short scale of the Freiburg Mindfulness Inventory	Mindfulness		X	X	X
Secondary Outcomes					
Patient Health Questionnaire	Depression		X	X	X
Generalized Anxiety Disorder Questionnaire	Anxiety		X	X	X
Short Form Perceived Stress Scale	Stress		X	X	X
World Health Organization Well-Being Index	Well-being		X	X	X
Body Perception Questionnaire	Interoceptive Sensibility		X	X	X
Emotion Regulation Questionnaire	Reappraisal and suppression		X	X	X
Toronto Alexithymia Scale	Alexithymia		X	X	X
Heartbeat perception task	Interoceptive Accuracy		X	X	X
Cortisol & DHEA	Psychobiological stress level		X	X	X
Covariates					
Demographic variables	E.g., weight, height, psychotherapy		X		
Previous experience with mindfulness, time spent practicing mindfulness and use of additional treatment options	Self-reported mindfulness and treatment experience		X	X	X
Genotype FKBP5 (rs1360780)	Gen x environment interaction		X		
Client Expectancy Questionnaire	Treatment expectancy and rationale credibility		X		
Dropout	Intervention adherence		X	X	
Client Satisfaction Questionnaire	Intervention satisfaction			X*	
Inventory for the Assessment of Negative Effects	Potential adverse effect			X*	

Note. * only for the intervention group

Sample size estimation

The sample size estimation based on a calculation of G*Power 3.1.9.2, assuming a small effect size of f = .15 (consistent with d = .3) in a repeated measurement model and a comparison of two groups. Based on an α-level of .05 and power of .90, the total sample should consist of 120 participants including 60 for the guided intervention group and 60 for the waitlist control group. The assumed effect size of d = .3 is based on the meta-analysis of Jayewardene, Lohrmann et al. [66] and Spijkerman et al. [65] regarding online mindfulness-based interventions.

Ethics and dissemination

All study procedures were approved by the ethics committee of Ulm University (application No. 48/18). The trial was registered prior to the recruitment at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register (DRKS; ID: DRKS00014701). Participants received written information on study conditions, data security, participation being voluntary and the right to leave the study at any time. To confirm understanding, written consent is obtained from all participants prior to study entry. Data collection is pseudonymized and only accessed by authorized study personnel obliged to secrecy. The results will be published in peer-reviewed journals and presented on international conferences.

Statistical analyses

All statistical analyses will be conducted according to the Intention-To-Treat (ITT) principle. Procedures of imputation will be chosen based on patterns and mechanism of missingness (e. g., by multiple imputations). Additionally, per protocol analyses will be performed to examine the impact of dropouts on study results. The significance level for all analyses will be $p \leq .05$ and will be adjusted for multiple comparisons using the Holm-Bonferroni correction method.

Standardized mean differences with 95% confidence intervals will be calculated post-treatment and follow-up to analyze between-group effect sizes. Regression analyses will be performed as a primary method, using linear regression for dichotomous outcomes. Based on the data structure, regression analysis will be adjusted accordingly (e.g., use of robust estimation or use of multilevel regression analysis in case of substantial intra-class correlation). Analyzed variables will include the covariates (e.g., age, gender, gene FKBP5) using path modeling.

Discussion

This study protocol describes the study design of a randomized controlled trial that investigates psychobiological health-related variables in addition to the commonly used self-report data of a guided online mindfulness-focused intervention in a student sample. We assume that individuals who participate in the guided intervention will show decreased depression, anxiety

and stress levels as well as reduced alexithymia in comparison to the waitlist control group. Furthermore, we hypothesize an increase of well-being, interoceptive sensibility and emotion regulation in the intervention group. Focusing on different psychobiological variables (interoceptive accuracy, hair cortisol, and DHEA) we expect similar positive effects. In order to find out more about the covariates, we also include sociodemographic data, the gene FKBP5, and expectations regarding the intervention in our analyses.

Our study focuses on some aspects discussed in previous studies, aiming at combining these points here. Consequently, this study has several strengths:

(1) Combination of self-report and psychobiological measurements

In comparison to earlier studies, our investigation includes self-report and psychobiological markers. Consequently, we use subjective as well as objective parameters to emphasize our results, meaning that especially psychobiological markers are less biased compared to the self-report measurements. Nonetheless, research so far showed that a combination of both is suitable to include advantages and disadvantage of both approaches [67, 68, 134]. Furthermore, the hair stress markers represent longitudinal markers from the last weeks or even months [80]. In contrast, cortisol measurements such as salivary, plasma or urine are time-limited and depend on changes associated with circadian rhythm regulation.

(2) Procedures to improve the adherence level

Our proposed intervention includes different opportunities to improve adherence. This is based on the high dropout rates of 40 to 70 percent in different online or smartphone interventions [61, 135, 136]. Firstly, we only include participants with low or moderate mindfulness in our intervention. One reason for choosing this level is a potential higher motivation and interest from partipants, resulting in an assumed lower dropout rate in the intervention. However, it should be mentioned that it is only a hypothesis, which is not measured in the study. Secondly, we use different modes of delivery in order to increase the adherence level of our online intervention. These modes include text, audio files, self-reflection, homework, instructions, and tips for implementing and transferring intervention components into daily life. Following the main seven intervention modules, participants also get two booster sessions, which summarize and repeat the other modules before. Thus, a moderate to long-term intervention effect is obtained, and the adherence level is expected to be high. Thirdly and importantly, we include e-coaching in our training. A current study of Kvillemo and co-workers [61], report that a higher contact level decreases the dropout rate and is an important option that increases the adherence level of participants. The e-coach has the task to give the participants feedback concerning the completed modules and remind them if they do not attend. Additionally, participants get

the opportunity to contact the e-coach via the messenger system of Minddistrict. Lastly, the online mindfulness-focused intervention is tailored to the particular needs of students, which will expect will raise the adherence level and likely enhance the effectiveness of the online intervention.

(3) Adherence level

To explore the reasons for different adherence levels, participants answer quantitative and qualitative questions regarding the content of modules and their motivation. These responses will help us to adapt and improve the online intervention and accordingly enhance adherence.

(4) Follow-up measurements six months after randomization

Several studies reported no follow-up measurements [61, 63, 64, 137]. Other studies used different intervals for the follow-up measurement after the intervention, ranging from two weeks up to six months [29, 44, 62, 135, 138]. To focus on the longitudinal effects of our intervention, we examine participants again six months after randomization.

Assuming positive results of the present online mindfulness-focused intervention, it could be a helpful opportunity for universities to establish such time and cost-effective healthcare services. Given the high stress rate in the student population, the present intervention will contribute information and practices to decrease individual's stress levels as well as to improve mental health in general. Another advantage is the prevention of other upcoming mental health problems, resulting from a high stress level. Thus, this stand-alone intervention can provide advantages for users and the health care system. Moreover, results will have implications for researchers, health care providers and public health policymakers.

Authors' contributions

DS, AMK, DDE, HB, and OP initiated this study. DS, AMK, AK, HB, and OP contributed to the design of this study. DS, AMK, CS, and FW adapted the intervention content and the assessment. DS and CS are responsible for recruitment. AK performed FKP5 genotyping and provided a methodology for the collection of hair and sample preparation for steroid analysis. He supervised all stages of biological assessments and analyses. DS wrote the draft of the manuscript. All authors contributed to the further writing of the manuscript and approved the final version of the manuscript.

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Competing interests statement

None declared.

Author Contributions

DS, AMK, DDE, HB, and OP were involved in the development of "StudiCare Mindfulness" or its predecessor versions. HB reports having received consultancy fees and fees for lectures/workshops from chambers of psychotherapists and training institutes for psychotherapists in the e-mental-health context. DDE reports having received consultancy fees/served in the scientific advisory board from several companies such as Minddistrict, Lantern, Schoen Kliniken and German health insurance companies. He is a stakeholder of the Institute for health training online (GET.ON), which aims to implement scientific findings related to digital health interventions into routine care.

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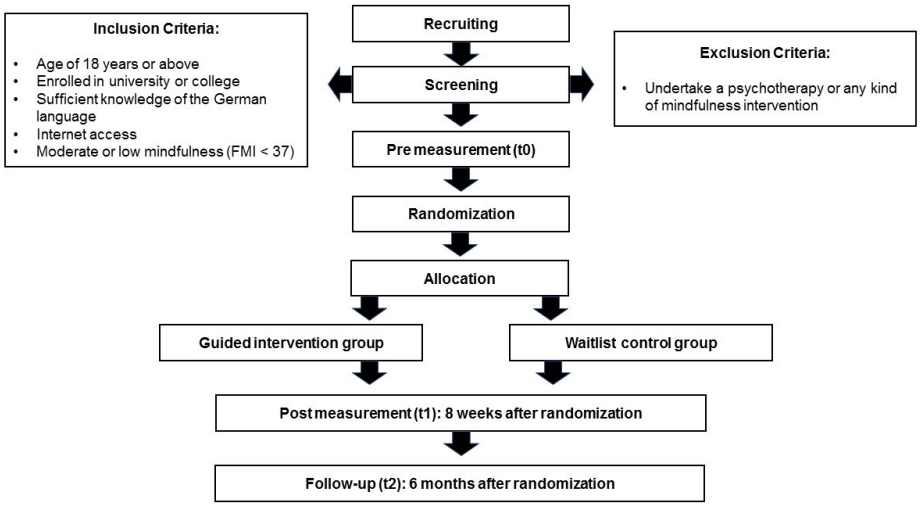
Figure caption:

Figure 1. Flow chart of the study design



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Effectiveness of a guided online mindfulness-focused intervention in a student population: Study protocol for a randomized control trial

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Abstract

Background: Previous studies show that university students experience higher psychological stress than the general population, resulting in increased vulnerability for mental disorders for the student population. Online mindfulness interventions will be delivered to students as a potentially promising and more flexible approach compared to face to face intervention with the aim of improving their mental health. This study purposes to investigate the effectiveness of a guided online mindfulness-focused intervention for university students by using both self-reported and psychobiological measures.

Methods and analyses: In this multicenter, two-armed randomized controlled trial (RCT) with a parallel design, a guided version of the online mindfulness-focused intervention "StudiCare Mindfulness" will be compared to a waitlist control group. In total, 120 participants will be recruited at different universities (of Applied Sciences) in (Neu-) Ulm. Data will be assessed prior to randomization, after eight weeks (post-intervention) and six months after randomization (follow-up). The primary outcome measure is mindfulness. The secondary outcome measures include depression-, anxiety- and stress level, well-being, interoceptive sensibility, emotion regulation and alexithymia. Psychobiological parameters comprise interoceptive accuracy, hair cortisol, and FKBP5 genotype. Sociodemographic variables, treatment expectations, side, and adverse side effects, as well as intervention satisfaction and adherence will be assessed. All data analyses will be conducted according to the Intention-To-Treat (ITT) principle.

Ethics and dissemination: All study procedures have been approved by the ethics committee of Ulm University (application No. 48/18). The findings will be disseminated widely through peer-reviewed publications and conference presentations.

Trial registration and status: The trial is registered at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register: DRKS00014701 (registration date: 07th May 2018; URL: https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00014701). In case of important protocol modifications, trial registration will be updated. This is protocol version number 1, 4th July 2019.

Keywords: RCT, eHealth, online intervention, stress, mindfulness, effectiveness, psychobiological measures

Strengths and limitations of this study

- "StudiCare Mindfulness" is an online mindfulness-focused intervention program with the aim to increase mindfulness and simultaneously decrease stress level in order to reduce mental disorders in university students.

- This study considers psychobiological parameters in addition to the common participants´ self-report data prior to randomization as well as eight weeks and six months after randomization.
- A follow-up measurement six months after randomization is administered.
- Because of the use of psychobiological parameters, the study will only be conducted at universities (of Applied Sciences) in (Neu-) Ulm, which could reduce generalizability.

Background

Stress is highly prevalent among university students. Previous studies showed that compared to the general population, students have significantly higher stress levels [1–3]. The increased clinical levels of stress in university students has been linked to a range of stressors such as new experiences and challenges in addition to new social relationships, academic pressures and exams [2, 4–7]. Moreover, such high stress levels have the potential to trigger a new mental illness such as anxiety and/or depression or exacerbate a pre-existing mental health condition [8–14]. For example, Auerbach and co-workers [15] found in an international WHO-survey that more than 20 percent of university students reported a mental disorder. However, it should be noted that 83 percent of these students had a mental illness onset before commencing their studies. Similar results were found in another survey, indicating that 23 percent of the university students met the criteria for a mental disorder [16]. The development of a mental disorder is related to a more severe and chronic disease trajectory, a higher risk to develop comorbidities, decreased academic performance, as well as an increased probability for dropouts during the university career [5, 9, 17–19].

Accordingly, it is crucial to prevent elevated stress levels to reduce the risk of university students developing a mental health disorder. In this context, previous studies revealed that most university students do not use face-to-face interventions and do not seek professional help, although most of the universities provide free health and counseling services [8, 20–26]. Prohibitive factors to accessing services reproted by university students included: lack of time, fear of stigma, the preference to get help and support from family or friends as well as lack of knowledge regarding available services at the university. Thus, internet- and mobile-based psychological interventions (IMIs) may offer a promising approach to close the gap between these barriers and to provide additional advantages (e.g., no need of therapist availability, low-threshold access, stigma-reduction, cost-effectiveness as well as flexibility regarding time and place) [22, 23, 27–31]. Emerging evidence from different studies has also demonstrated that online interventions can be as effective as face-to-face programs in healthy and clinical populations [32–34]. Furthermore and most importantly, nowadays young people grow up in a digital world and prefer using the internet as well as smartphones daily [35–37]. They are also searching for health information online [38]. However, a study with an Australian sample (mean age 36.6 years) showed that 77.1% prefer face-to-face intervention [39]. In another study by Ryan and colleagues [26], findings indicate that nearly 50% of university students (mean age 23.7) in Australia have a preference for online interventions. Consequently, the age range and the context seems to be crucial for understanding the preferences of the type of therapy delivery in students, [26].

Moreover, Stallman and Kavanagh [40] as well as Ebert and co-workers [27], observed that university students show a high acceptance and usability for online interventions. A growing body of research found that online interventions are helpful to improve mental health conditions [27, 41–46]. These effects can be enhanced by therapeutic guidance, meaning that additionally participants receive support from an expert, either online or face-to-face whilst receiving their online intervention [6, 47].

One opportunity to improve mental and physical health is mindfulness. Mindfulness is the awareness of the present moment in an open, accepting and non-judgmental way with the focus on internal bodily signals (e.g., ones' breathing and other bodily sensations [48–50]) as well as external stimuli (e.g., sounds, pictures, behavior [51]) . Several studies found positive effects of a mindfulness-based intervention on mental and physical health conditions, independent of whether these included healthy or clinical participants [52–60]. Furthermore, Wahbeh and colleagues [60] found in their study sample that there was a preference for online mindfulness-based interventions compared to group or one-by-one interventions. As there are clear benefits of mindfulness based interventions as well as as online interventions such as e-health programs, it seems timely to combine these approaches to reduce stress and therefore to improve mental health in a student population.

Numerous studies [44, 61–64] and meta-analyses [65, 66] found evidence for the efficacy of online mindfulness-based interventions with the focus on self-reported health variables (e.g., depression, anxiety, and stress). For example, Spijkerman, Pots and Bohlmeijer [65] compared 15 randomized control trials and showed small to medium effect sizes regarding the reduction of anxiety (g = .22; 95% CI: .05 - .39), improvement of depression (g = .29, 95% CI: .13 - .46), well-being (g = .23; 95% CI .09 - .38) and mindfulness (g = .32, 95% CI .23 - 42) in healthy samples as well as samples with mental disorders. Especially for stress reduction a large effect was shown (g = .51; 95% CI: .26 - .75). Similar results were found in another meta-analysis conducted by Jayewardene, Lohrmann, Erbe, and Torabi [66]. The authors compared eight studies focusing on the effects of online mindfulness interventions in populations with subclinical mental health conditions in non-clinical populations (g = .28 - .42; 95% CI: .15 - .67). Moreover, these results showed further improvements in mental health at follow-up (g = .47 - .70; CI: .14 - 1.13). Even though these findings are promising, self-report data might substantially overestimate the effectiveness of interventions. Hence, the field should move forward to include more objective data, to verify the promising results, by including assessments of psychobiological variables.

Until now, there are no studies regarding the effectiveness of online mindfulness-focused training on psychobiological variables, which represent objective markers of mental health conditions. Such variables are not influenced by social desirability, memory problems or a

conscious perception [67]. Consequently, psychobiological data provide additional markers to complement the self-reported data and should, therefore, be included in mindfulness and stress-related intervention studies. In this study, we will include psychobiological measurements of interoceptive accuracy as well as cortisol and dehydroepiandrosterone (DHEA). Interoceptive accuracy represents the behavioral assessment of an individual's ability to perceive internal bodily changes, which is mostly assessed via the heartbeat perception task [68]. Moreover, interoceptive accuracy is associated with other health-related variables such as emotion perception and regulation, alexithymia, stress, depression, anxiety symptoms, and eating behavior [69–74] and can be influenced by the mentioned health-related variables. Recent studies focusing on interoceptive accuracy have shown mixed results regarding the impact of different offline mindfulness interventions [75–77].

Two biological indicators of the body's physiological stress response are cortisol and DHEA. While cortisol is a steroid hormone released by the hypothalamic-pituitary-adrenalin (HPA) axis in response to stress [78], DHEA represent an endogenous steroid hormone on the stress response that can antagonize the effect of cortisol [79]. To assess long-term effects of stress, collecting hair samples is superior to fluid biomaterial (e.g., saliva, blood), because hair samples reflect the stress level of weeks or even months and are not influenced by acute stress before or during the measurements or body's circadian rhythm as well as hormone level [80–83]. Accordingly, the ratio between cortisol and DHEA seems to be important. There is only one study showing positive effect of a 8-week body scan training (one approach of the mindfulness-based stress reduction program) on cortisol, DHEA and the ration [84]. Several other studies reveal inconsistent results concerning the effect of mindfulness interventions on stress parameters assessed by saliva or plasma cortisol [85–90]. Moreover, there is no other evidence in previous research of mindfulness training on DHEA. However, some studies measured the sulfated form of DHEA (DHEA-S) and found no effect on DHEA-S after an 8-week mindfulness-based stress program in a population diagnosed with cancer. To combine both stress markers, different researchers suggest the cortisol/DHEA ratio as a parameter for the endocrine imbalance of HPA regulation [91–95]. Comparable with DHEA, there is only one study that has investigated the cortisol/DHEA-S ratio. It indicated that men diagnosed HIV-positive had an improved ratio after participating in a cognitive-behavioral stress management program in comparison to a waitlist control group [94]. To sum up, studies examining psychobiological parameters in mindfulness-based programs are very sparse, though there are some promising results. Nonetheless, such investigations are essential to characterize the long-term effects of mindfulness on psychobiological processes.

Another interesting marker is the gene FKBP5 coding for FK506 binding protein 51 (FKBP51). FKBP51 is a co-chaperone of the glucocorticoid receptor, changing its affinity for cortisol and therefore influencing the reactivity of cortisol-mediated stress signaling in

the body. Compared to C-allele carriers (wild type) at position rs1360780, individuals with the T-allele show a higher risk for depression and less clinical responsiveness to antidepressant treatment [96]. Also, T-allele carriers show more pronounced changes in hair cortisol levels with increasing childhood maltreatment compared to C-allele carriers, demonstrating a gen x environment interaction with a dose-response relationship between adverse childhood experiences, a strong predictor for late-life depression, and steroid hormones of the body's stress response [97]. In comparison to the other psychobiological stress marker, FKBP5 can only be assessed once, because there is no fluctuation. Consequently, this marker will be included as a covariate variable.

An additional focus of the present trial is the effectiveness of guidance during the online mindfulness-focused intervention. Research in this context provides evidence that guided online intervention enhances the efficacy of health-related variables [65, 98]. In the context of online mindfulness training for students, only the study of Mak and colleagues [62] provided telephone or email support without a control group.

Taken together, we hypothesize that

1) The primary outcome mindfulness will be improved after the intervention in comparison to a waitlist control group.
2) The secondary outcomes of depression, anxiety, stress level, interoceptive sensibility, emotion regulation, and alexithymia will also be improved. We assume similar results for the psychobiological variables (secondary outcomes), including interoceptive accuracy (assessed via the heartbeat perception task) as well as cortisol and DHEA levels in hair.

Further, it should be noted that outcomes can be influenced by various covariates. For example, interoceptive accuracy can be influenced by emotion regulation, alexithymia or depression and anxiety symptoms [69, 72–74]). Therefore, we will test for potential effect-modifying variables on an exploratory level. Lastly, we intend to explore and analyze the participants' satisfaction, adherence and acceptance of the intervention.

Methods

Study design

This project is a two-armed randomized controlled trial with a parallel design comparing the effectiveness of a guided version of the online, preventive mindfulness intervention "StudiCare Mindfulness" to a waitlist control group (see Fig. 1 for flowchart). The research aims to examine the effectiveness of StudiCare Mindfulness on different self-reported and psychobiological health-related parameters at three measurement points (before the intervention as well as eight weeks and six months after randomization). Moreover, the individuals' adherence,

acceptance, and satisfaction are measured to identify possibilities to improve the intervention. Participants of both the control and the intervention group have access to treatment as usual. Thus, participants can use other support or treatment options that will be monitored in order to control for potential confounding effects.

Two departments of the Ulm University are involved in the project, including the Department of Clinical and Health Psychology and the Department of Clinical Psychology and Psychotherapy. It should be noted that this is a cooperation project. Besides the presented study in this protocol, there is another parallel mindfulness trial, investigating the effectiveness of a "guidance on demand" and an unguided version of "StudiCare Mindfulness" in comparison to a waitlist control group [99].

The present study is conducted and will be reported according to the CONSORT 2010 Statement [100] and the guidelines for executing and reporting internet intervention research [101]. The study protocol complies with recommendations of the SPIRIT 2013 Checklist for clinical trial protocols [102].

The "StudiCare Mindfulness" trial is carried out as part of the "StudiCare" project funded by BARMER, a cooperation of the Universities of Erlangen-Nuremberg and Ulm. The overall project aims to improve college university students' well-being by evaluating their mental health in longitudinal panel surveys as well as developing and offering a broad assortment of internet-based interventions for psychological and behavioral issues (such as procrastination, exam anxiety, physical activity). It is embedded in the "World Mental Health Survey International College Student" project (WMH-ICS) [103] as well as the "Caring Universities" project [104].

Patient involvement

University students as target end users of StudiCare Mindfulness were involved in the development process of the intervention. They will also be involved in the conduct and the reporting of the research, however, not in their role as end user but in their role as scientists. The public will be informed about the results on several ways, amongst others publications, lectures and workshops.

Eligibility criteria

Participants providing written informed consent as well as fulfilling the following inclusion criteria for participation will be applied: a) age of 18 or above, b) enrolled at Universities (of Applied Sciences) in Ulm or Neu-Ulm, c) sufficient knowledge of the German language, d)

internet access, e) moderate to low mindfulness (Freiburg Mindfulness Inventory FMI < 37); this cut-off was chosen as it represents the medium value of the FMI in subjects from the general population [105]. Participants are excluded from the study if they currently undertake psychotherapy or any mindfulness intervention. To investigate if participants are eligible, they have to fill out a screening questionnaire.

Setting/Recruitment

Recruitment has started in May 2018 and will continue until the target sample size of 120 participants will be reached. Participants are recruited from particular different universities in (Neu-) Ulm, including Ulm University, Ulm University of Applied Sciences and Neu-Ulm University of Applied Sciences because psychobiological parameters have to be assessed on-site. The following recruiting channels are used: email, flyer and poster, social media, student unions, and student counseling services. University students get information about the "StudiCare" offers and a link to the homepage (www.studicare.com), where they can get further information and register for the IMIs. Once registered, they receive an email with a link to the screening questionnaire. Depending on the location of their University, participants are either allocated to Kuechler et al.'s trial [99] (all other cooperating universities in Germany, Austria and Switzerland) or to the present study (students from different universities (of Applied Sciences) in Ulm and Neu-Ulm), as psychobiological tests demand actual attendance on-site). Once the screening is completed, participants receive an email with further information on the study as well as an informed consent form, which they are required to send back to the study staff via email. When written consent is obtained and the pretest completed, another email is sent to inform participants about their group (intervention or waitlist control group). If participants are part of the intervention group, they will also receive a link to the intervention. Participants are informed that "StudiCare Mindfulness" cannot replace psychotherapy and are recommended to seek counseling/psychotherapy in case of distinctive mental health problems. Additionally, they are provided with alternative treatment options and contact details (this information is also given to participants who do not meet the selection criteria).

Randomization

After completing the baseline assessment, participants are randomly allocated to one of two study groups (guided vs. waitlist control group) by an independent member of the Ulm University not otherwise involved and therefore blinded to all processes of the study. Via an automated, online-based randomization program (www.sealedenvelope.com), permuted block randomization is performed with an allocation ratio of 1:1 and variable block sizes of 2 and 4 (randomly arranged).

Intervention

The online mindfulness-focused intervention consists of seven weekly, target-group-specific modules of approximately 60 min. each. Additionally, two booster sessions are activated four and twelve weeks after completion of the seventh module in order to enhance the sustainability of intervention effects. These booster sessions include a summary of the seven previous modules. Our aim was to give participants the possibility to collect a repertoire of useful methods. Beyond that, already completed sessions are accessible and can be repeated as often as participants wish to. All modules contain information on stress, well-being, and mindfulness with a weekly alternating focus on different topics such as interoception, dysfunctional and beneficial thinking, values and goals. Whereas these contents are provided via texts, images and interactive elements (such as quizzes or conditional content), the focus of the intervention lies on the regular practice of mindfulness exercises such as body-scans, breathing meditations or mindful yoga. Therefore, each module includes downloadable audio files as well as mindfulness diaries to be completed in weekly homework assignments. At the beginning of each module, participants are encouraged to reflect on their assignments and also on their most and least mindful moments of the week. The content of the intervention is mainly based on Acceptance and Commitment Theory [106] as well as mindfulness-based stress reduction [107] and also includes some elements of stress management [108] and cognitive-behavioral therapy. We summarized the different methods as one mindfulness-focused intervention.

The intervention's primary goal is to increase the student participants' mindfulness and psychological flexibility in order to enable them to manage their daily hassles flexibly. Furthermore, the intervention was developed by the Department of Clinical Psychology and Psychotherapy, Ulm University. Its efficacy has already been demonstrated in a randomized controlled trial [109]. Based on participants' feedback the different sessions were adapted and further refined. Moreover, the two weekly sessions ("Mindfulness body perception" and "Body and sense") were also extended. Table 1 summarizes the topics and contents of each module. The intervention is available for participants on the Minddistrict platform (www.minddistrict.com), a company specialized in the provision of internet-based health interventions. Participants can get access to the platform via their personal username and password on a 24/7 basis. All transferred data will be secured based on ISO27001 and guidelines NEN7510.

Table 1. Overview of the different topics and contents of each module

Module	Aims and content	Examples of exercises and assignments
1. Being in the here and now	Introducing the concept of mindfulness	Reviewing most and least mindful moments of the day; practicing Body Scan; taking mindful walks
2. Mindful body perception	Practicing awareness of body signals	Testing one's heartbeat perception; practicing "heart meditation"; mindful eating and drinking
3. A new perspective on stress	Distancing oneself from stress-inducing thoughts	Identifying former ways of coping with stress; learning techniques to challenge automatic thoughts; meditation exercise
4. Developing beneficial thoughts	Getting to know alternative ways of thinking	Identifying one's "stress patterns" and developing and internalizing beneficial thoughts; practicing breathing meditation
5. What makes your life valuable?	Identifying one's values and pursuing one's goals	Writing a speech for one's 70th birthday; setting and pursuing goals with the SMART technique; meditation exercise
6. Being mindful towards yourself	Learning how to accept one's personality traits appreciatively	Exercise to identify different personality traits and corresponding automatic reactions; learning to accept and appreciate all personality traits
7. Training your body and senses	Exercising the ability to enjoy and getting acquainted with the practice of yoga	Mindful chocolate eating exercise; mindful yoga exercises
Booster-Session 1 (4 weeks after completion of module 7)	Repeating module 1 to 3 and mindfulness exercises	Choosing favorite mindfulness exercises; setting goals for their implementation in the coming weeks
Booster- Session 2 (12 weeks after completion of module 7)	Repeating modules 4 to 7 and ensuring long-term integration of mindfulness into daily life	Reviewing pursuit of goals in the last two months; identifying potential barriers and developing solutions

Guidance and promotion of adherence

Participants randomized to the intervention will receive support by an e-coach. They can contact their e-coach in case of questions or if they wish to get feedback for any of their completed modules. E-coaches are trained and supervised psychologists (by HB, AMK) psychologists that give semi-standardized feedback after participants finish their modules within two working days, following an e-coach manual. Whenever participants have questions or wish to get feedback on their module input, they can contact their personal e-coach via the Minddistrict' platform's message function. At the beginning of the intervention, each participant receives a welcoming message in which their e-coach introduces himself. Additionally, the first module explicitly highlights the possibility to contact the e-coach at any time. The feedback content is specific to the participants' assignments in order to support treatment adherence. It also includes positive reinforcement to encourage and motivate the participants to continue the intervention. E-coaches are instructed to document any responses to questions or give

feedback. This will enable the evaluation of actual usage of a guided intervention by participants.

Control condition

Participants in the waitlist control group have unrestricted access to any usual treatment options. They receive an information leaflet informing them about alternative support options such as university counseling services, psychotherapy or helplines as well as the advice to seek help in case their well-being declines. Six months after randomization, participants of the control condition receive the unguided version of the intervention.

Assessments and outcomes

Assessments take place before (t0; pre-measurement) as well as after eight weeks (t1; post measurement) and six months (t2; follow-up) after randomization. All self-report data are collected using the online survey platform "Unipark" (www.unipark.de). Furthermore, participants come to the laboratory of the department Clinical and Health Psychology to collect the psychobiological data (heartbeat perception task, hair samples for cortisol and DHEA as well as buccal cell swabs for the collection of DNA from buccal mucosa for genotyping FKBP5). Biological samples are processed in the Department of Clinical & Biological Psychology directly under the supervision of AK. To get an overview of the different outcome measures and assessement time points see table 2. Participants receive 20 EUR or 3 course credits compensation for the laboratory assessment. Importantly, they do not obtain any compensation for participation in the intervention.

*** Please insert Figure 1 here ***

Primary outcome: Mindfulness

The 14-item short scale of the Freiburg Mindfulness Inventory (FMI) [105, 110] is used to derive a mindfulness score. The FMI consists of a 4-point Likert scale ranging from 1 = "rarely" to 4 = "almost always". The short scale is sensitive to changes and appropriate for investigating subjects without meditation experience [105]. In a study by Heidenreich, Ströhle, and Michalak [111], a high internal consistency with a Cronbach's Alpha of 0.84 was shown.

Secondary outcomes

Depressive symptoms. The depression module of the Patient Health Questionnaire (PHQ-9) [112] comprises nine items that are rated on a 4-point Likert scale (0 = “not at all” to 3 = “nearly every day”). The PHQ-9 is a widely used depression screening that has demonstrated validity and good diagnostic properties (sensitivity of 0.95 and specificity of 0.84) and internal consistency (α = .89) [113].

Anxiety. The Generalized Anxiety Disorder Questionnaire (GAD-7) [114] consists of a 7-item anxiety scale ranging from “not at all” (= 0) to “nearly every day” (= 3) and is used to screen for generalized anxiety disorder. Evaluations of the questionnaire show a sensitivity of 0.89, specificity of 0.82 and a good test-retest reliability (intraclass correlation = .83). The GAD-7 has been identified as a reliable and valid measure of anxiety in the general population with Cronbach's alpha of .89 [115].

Stress. The Short Form Perceived Stress Scale (PSS-4), derived from the Perceived Stress Scale [116], is used to measure the participant’s perceived stress as the degree to which situations in one’s life are rated as stressful (scale ranging from 0 = “never”, 4 = “very often”). The psychometric properties of the PSS-4 are acceptable and reliable across cultures, with Cronbach’s alpha of .77 [117].

Well-being. The well-established 5-item World Health Organization Well-Being Index (WHO-5) [118] is used to assess subjective psychological well-being. The response scale refers to the frequency of relevant feelings over the past two weeks ranging from “*at no time*” (= *0*) to “*all of the time*” (= *5*). With a sensitivity of 0.86 and specificity of 0.81, WHO-5 is a screening tool for depression, which has been demonstrated among several clinical studies. Applicability across study fields and clinical validity is very high [119].

Interoceptive sensibility. Interoceptive sensibility (IS) is assessed by the awareness section of the Body Perception Questionnaire (BPQ) [120]. It includes 45 items of individual identifications of bodily signals on a 5-point Likert scale, ranging from “never” (= 1) to “always” (= 5). Calculated t scores reflect a standardized value according to a normal distribution based on a mean of 50 and a standard deviation of 10. Previous reliability reports exist only for the short form of the Body Perception Questionnaire [121], showing a categorical omega coefficient between .68 and .97. and a high retest reliability.

Emotion regulation. A German translation [122] of the Emotion Regulation Questionnaire (ERQ) [123] is used to assess individual differences in the habitual use of two emotion regulation strategies, reappraisal and suppression. The questionnaire includes six items measuring reappraisal and four items measuring suppression. Participants are required to indicate whether they agree with each statement on a 7-point Likert scale ranging from 1 (=

"strongly disagree") to 7 (= "strongly agree"). The ERQ demonstrates good scale score reliability for the suppression (Cronbach's alpha = .76) as well for the reappraisal factors (Cronbach's alpha = .74) [122].

Alexithymia. The Toronto-Alexithymia Scale (TAS-20) [124]; German adaptation by Kupfer et al. [125]) measures alexithymia. The questionnaire consists of 20 items rated on a five-point Likert scale (1 = "strongly disagree"; 5 = "strongly agree") with total scores ranging from 20 to 100, reflecting three-factor scales: "difficulties identifying feelings" (DIF), "difficulty describing feelings" (DDF) and "externally oriented thinking" (EOF). Higher scores on the different subscales indicate higher levels of alexithymia. The TAS-20 is a valid instrument with good internal consistency (Cronbach's alpha of 0.85 to 0.86) and test-retest reliability [126].

Subjective side effects and adverse events. In a survey with 195 former psychotherapy patients, 94 % stated to have experienced negative effects during or after psychotherapy [127]. Consequently, Ladwig and co-workers [127] developed the Inventory for the Assessment of Negative Effects (INEP), which is included to assess any changes in the experiences during or after the treatment in the social and/or work environment and whether they are attributed to the psychotherapeutic intervention. The items cover potential adverse events in the personal, intrapersonal and social context (e. g. "emotions", "family and friends"). Four items are rated on a 7-point bipolar scale (-2 = "worse", +3 = "better"), the others are rated on a four-point scale (0 = "no agreement", 3 = "full agreement"). The present trial uses an adapted 22-item version covering possible negative effects associated specifically with online-training (e.g., concerns about data protection). The original scale has demonstrated high internal consistency with a Cronbach's alpha of 0.86 [127].

Intervention satisfaction and adherence. The Client Satisfaction Questionnaire (CSQ) [128] is a validated 8-item tool and is used in a German version adapted for the evaluation of IMIs (ZUF-8) [129]. The CSQ-8 comprises eight items, each with a 4-point scale of specific response alternatives (e. g. 1 = "quite unsatisfied", 4 = "very satisfied"). Good psychometric properties have been demonstrated including Cronbach's alphas between .88 and .92 [130]. Additionally, qualitative feedback is assessed via a self-developed questionnaire for further optimization of the intervention. Adherence is operationalized by the number of modules participants complete during the "per protocol" intervention period of eight weeks.

Psychobiological outcomes

We also assess psychobiological variables including the heartbeat perception task (= interoceptive accuracy) as well as hair cortisol and DHEA at all three measurement points. The

FKBP5 genotype dichotomous model (CC vs. CT/TT carriers) is only assessed at the pre-measurement and is used as a covariate in the analyses.

Heartbeat perception task. The heartbeat perception task by Schandry [131] assesses the sensitivity for cardiovascular signals, namely interoceptive accuracy. Therefore, participants are instructed to listen to their own heartbeats and count them silently during four different intervals. We chose a training interval of 15 seconds for participants to get familiar with the task, followed by four test intervals (35, 45, 25 and 60 seconds). Importantly, participants do not get any information about the length of these intervals. They receive start and stop signals for each interval from the investigator. After every stop, they have to report their counted heartbeats as well as their confidence ratings regarding them (1 = "total guess/no heartbeat awareness" to 10 = "complete confidence/full perception of heartbeat"). Biopac MP 150 (sampling rate 1000 Hz) is used for recording.

Hair cortisol and DHEA. To assess the changes in the psychophysiology stress level across the time of intervention, cortisol and DHEA are used. Therefore, two strains (~ 3 mm diameter) with a length of minimum 2 cm are obtained from the posterior vertex of each participant. Importantly, hair should be cut as close to the scalp as possible, using a fine medical scissor. The scalp hair is wrapped in aluminum foil and stored at -20°C in a dry, dark place until the analyses start.

Gene FKBP5. For the investigation of a possible gen x environment interaction, the FKBP5 genotype is included as another psychobiological variable in the study. Therefore, samples from the buccal mucosa are taken non-invasively using buccal mucosa collection swabs (Salimetrics, UK). DNA from buccal cells is isolated using commercially-available column-based purification techniques (Qiagen, Germany). DNA is tested for quality (260/280 nm absorption) and concentration (Qubit, Thermofisher, USA). TaqMan assays for FKBP5 genotyping at position rs1360780 (T/C-allele) are performed using qPCR technology on a QuantStudio6 machine (Thermofisher, USA).

Covariates. To investigate potential effect-modifying influences [132], several sociodemographic variables are assessed: age, gender, nationality, marital status, study course and number of semesters, weight and height (= BMI), previous experience with mindfulness, time spent practicing mindfulness, psychotherapy experience and use of additional treatment options (such as psychological counselling or psychotherapy). Regarding the hair analyses, we evaluate current hair color and coloring, hair structure and existence of permanent waves. To examine the influence of treatment expectations on outcomes the Client Expectancy Questionnaire is used, which has demonstrated high internal consistency (α = 0.84-0.85; CEQ) [133]. It consists of six items which are measured on a 9-point Likert Scale

with higher scores representing positive expectations and credibility. Additionally, we collect data in the post-measurement of the online survey regarding the claim of other support (coaching, psychotherapy, psychiatry, family doctor, psychotropic drugs, mindfulness training, other health training or "StudiCare" projects). Further, if subjects participate in another kind of mindfulness training, they are asked for the format (presence, online, book, coaching).

Table 2. Summary of the outcome assessments and assessment time points

Variables	Measurement	Screening	T0	T1	T2
Inclusion and exclusion criteria					
Demographic variables	E.g., age, enrolled in a university, internet access, current participation in mindfulness intervention	X			
Short scale of the Freiburg Mindfulness Inventory	Mindfulness	X			
Primary Outcome					
Short scale of the Freiburg Mindfulness Inventory	Mindfulness		X	X	X
Secondary Outcomes					
Patient Health Questionnaire	Depression		X	X	X
Generalized Anxiety Disorder Questionnaire	Anxiety		X	X	X
Short Form Perceived Stress Scale	Stress		X	X	X
World Health Organization Well-Being Index	Well-being		X	X	X
Body Perception Questionnaire	Interoceptive Sensibility		X	X	X
Emotion Regulation Questionnaire	Reappraisal and suppression		X	X	X
Toronto Alexithymia Scale	Alexithymia		X	X	X
Heartbeat perception task	Interoceptive Accuracy		X	X	X
Cortisol & DHEA	Psychobiological stress level		X	X	X
Covariates					
Demographic variables	E.g., weight, height, psychotherapy		X		
Previous experience with mindfulness, time spent practicing mindfulness and use of additional treatment options	Self-reported mindfulness and treatment experience		X	X	X
Genotype FKBP5 (rs1360780)	Gen x environment interaction		X		
Client Expectancy Questionnaire	Treatment expectancy and rationale credibility		X		
Dropout	Intervention adherence		X	X	
Client Satisfaction Questionnaire	Intervention satisfaction			X*	
Inventory for the Assessment of Negative Effects	Potential adverse effect			X*	

Note. * only for the intervention group

Sample size estimation

The sample size estimation based on a calculation of G*Power 3.1.9.2, assuming a small effect size of f = .15 (consistent with d = .3) in a repeated measurement model and a comparison of two groups. Based on an α-level of .05 and power of .90, the total sample should consist of 120 participants including 60 for the guided intervention group and 60 for the waitlist control group. The assumed effect size of d = .3 is based on the meta-analysis of Jayewardene, Lohrmann et al. [66] and Spijkerman et al. [65] regarding online mindfulness-based interventions.

Ethics and dissemination

All study procedures were approved by the ethics committee of Ulm University (application No. 48/18). The trial was registered prior to the recruitment at the WHO International Clinical Trials Registry Platform via the German Clinical Studies Trial Register (DRKS; ID: DRKS00014701). Participants received written information on study conditions, data security, participation being voluntary and the right to leave the study at any time. To confirm understanding, written consent is obtained from all participants prior to study entry. Data collection is pseudonymized and only accessed by authorized study personnel obliged to secrecy. After data collection is completed, personalized information will be deleted and all data will be completely anonymized. The results will be published in peer-reviewed journals and presented on international conferences.

Statistical analyses

All statistical analyses will be conducted according to the Intention-To-Treat (ITT) principle. Procedures of imputation will be chosen based on patterns and mechanism of missingness (e. g., by multiple imputations). Additionally, per protocol analyses will be performed to examine the impact of dropouts on study results. The significance level for all analyses will be $p \leq .05$ and will be adjusted for multiple comparisons using the Holm-Bonferroni correction method.

Standardized mean differences with 95% confidence intervals will be calculated post-treatment and follow-up to analyze between-group effect sizes. Regression analyses will be performed as a primary method, using linear regression for dichotomous outcomes. Based on the data structure, regression analysis will be adjusted accordingly (e.g., use of robust estimation or use of multilevel regression analysis in case of substantial intra-class correlation). Analyzed variables will include the covariates (e.g., age, gender, gene FKBP5) using path modeling.

Discussion

This study protocol describes the study design of a randomized controlled trial that investigates psychobiological health-related variables in addition to the commonly used self-report data of

a guided online mindfulness-focused intervention in a student sample. We assume that individuals who participate in the guided intervention will show decreased depression, anxiety and stress levels as well as reduced alexithymia in comparison to the waitlist control group. Furthermore, we hypothesize an increase of well-being, interoceptive sensibility and emotion regulation in the intervention group. Focusing on different psychobiological variables (interoceptive accuracy, hair cortisol, and DHEA) we expect similar positive effects. In order to find out more about the covariates, we also include sociodemographic data, the gene FKBP5, and expectations regarding the intervention in our analyses.

Our study focuses on some aspects discussed in previous studies, aiming at combining these points here. Consequently, this study has several strengths:

(1) *Combination of self-report and psychobiological measurements*

In comparison to earlier studies, our investigation includes self-report and psychobiological markers. Consequently, we use subjective as well as objective parameters to emphasize our results, meaning that especially psychobiological markers are less biased compared to the self-report measurements. Nonetheless, research so far showed that a combination of both is suitable to include advantages and disadvantage of both approaches [67, 68, 134]. Furthermore, the hair stress markers represent longitudinal markers from the last weeks or even months [80]. In contrast, cortisol measurements such as salivary, plasma or urine are time-limited and depend on changes associated with circadian rhythm regulation.

(2) *Procedures to improve the adherence level*

Our proposed intervention includes different opportunities to improve adherence. This is based on the high dropout rates of 40 to 70 percent in different online or smartphone interventions [61, 135, 136]. Firstly, we only include participants with low or moderate mindfulness in our intervention. One reason for choosing this level is a potential higher motivation and interest from partipants, resulting in an assumed lower dropout rate in the intervention. However, it should be mentioned that it is only a hypothesis, which is not measured in the study. Secondly, we use different modes of delivery in order to increase the adherence level of our online intervention. These modes include text, audio files, self-reflection, homework, instructions, and tips for implementing and transferring intervention components into daily life. Following the main seven intervention modules, participants also get two booster sessions, which summarize and repeat the other modules before. Thus, a moderate to long-term intervention effect is obtained, and the adherence level is expected to be high. Thirdly and importantly, we include e-coaching in our training. A current study of Kvillemo and co-workers [61], report that a higher contact level decreases the dropout rate and is an important option that increases the adherence level of

participants. The e-coach has the task to give the participants feedback concerning the completed modules and remind them if they do not attend. Additionally, participants get the opportunity to contact the e-coach via the messenger system of Minddistrict. Lastly, the online mindfulness-focused intervention is tailored to the particular needs of students, which will expect will raise the adherence level and likely enhance the effectiveness of the online intervention.

(3) *Adherence level*

To explore the reasons for different adherence levels, participants answer quantitative and qualitative questions regarding the content of modules and their motivation. These responses will help us to adapt and improve the online intervention and accordingly enhance adherence.

(4) *Follow-up measurements six months after randomization*

Several studies reported no follow-up measurements [61, 63, 64, 137]. Other studies used different intervals for the follow-up measurement after the intervention, ranging from two weeks up to six months [29, 44, 62, 135, 138]. To focus on the longitudinal effects of our intervention, we examine participants again six months after randomization.

Assuming positive results of the present online mindfulness-focused intervention, it could be a helpful opportunity for universities to establish such time and cost-effective healthcare services. Given the high stress rate in the student population, the present intervention will contribute information and practices to decrease individual's stress levels as well as to improve mental health in general. Another advantage is the prevention of other upcoming mental health problems, resulting from a high stress level. Thus, this stand-alone intervention can provide advantages for users and the health care system. Moreover, results will have implications for researchers, health care providers and public health policymakers.

Authors' contributions

DS, AMK, DDE, HB, and OP initiated this study. DS, AMK, AK, HB, and OP contributed to the design of this study. DS, AMK, CS, and FW adapted the intervention content and the assessment. DS and CS are responsible for recruitment. AK performed FKP5 genotyping and provided a methodology for the collection of hair and sample preparation for steroid analysis. He supervised all stages of biological assessments and analyses. DS wrote the draft of the manuscript. All authors contributed to the further writing of the manuscript and approved the final version of the manuscript.

Funding statement

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Availability of data and materials

All principal investigators will be given full access to the data sets. Data set will be stored on password-protected servers of Ulm University with restricted access. External researches may get access to the final trial dataset on request depending on to be specified data security and data exchange regulation agreements. To ensure confidentiality, data dispersed to any investigator or researcher will be blinded of any identifying participant information.

Competing interests statement

None declared.

Author Contributions

DS, AMK, DDE, HB, and OP were involved in the development of "StudiCare Mindfulness" or its predecessor versions. HB reports having received consultancy fees and fees for lectures/workshops from chambers of psychotherapists and training institutes for psychotherapists in the e-mental-health context. DDE reports having received consultancy fees/served in the scientific advisory board from several companies such as Minddistrict, Lantern, Schoen Kliniken and German health insurance companies. He is a stakeholder of the Institute for health training online (GET.ON), which aims to implement scientific findings related to digital health interventions into routine care.

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Figure caption:

Figure 1. Flow chart of the study design

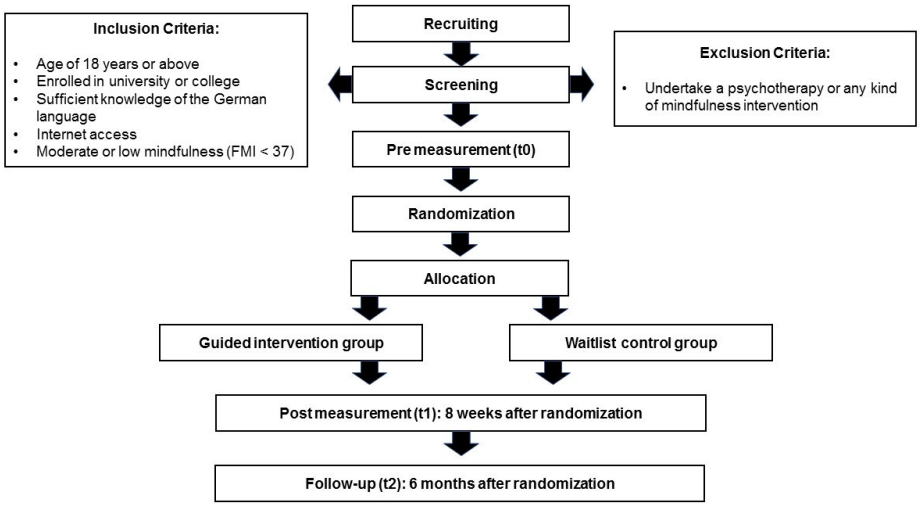

Figure 1. Flow chart of the study design

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,20
	5b	Name and contact information for the trial sponsor	-
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	-
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-7
	6b	Explanation for choice of comparators	4-7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7/8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9/12
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8/9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	-
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11/12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-16

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12, Fig. 1(Flowchart)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10/17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	-
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	-

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13,17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2/17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	2
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	27
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	-
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21

	31b	Authorship eligibility guidelines and any intended use of professional writers	-
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.